

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No. 7,195,751

TC/A.U.: 1626

Issued: March 27, 2007

Examiner: Nyeemah A. GRAZIER

Application No.: 10/765,267

Attorney Docket No.: 262_BP_0207_03_US

Applicants: Darryl J.C. PAPPIN et al.

Customer No.:85,173

Filed: January 27, 2004

Confirmation No.: 9577

Title: Compositions and Kits Pertaining to Analyte
Determination

ATTN: Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

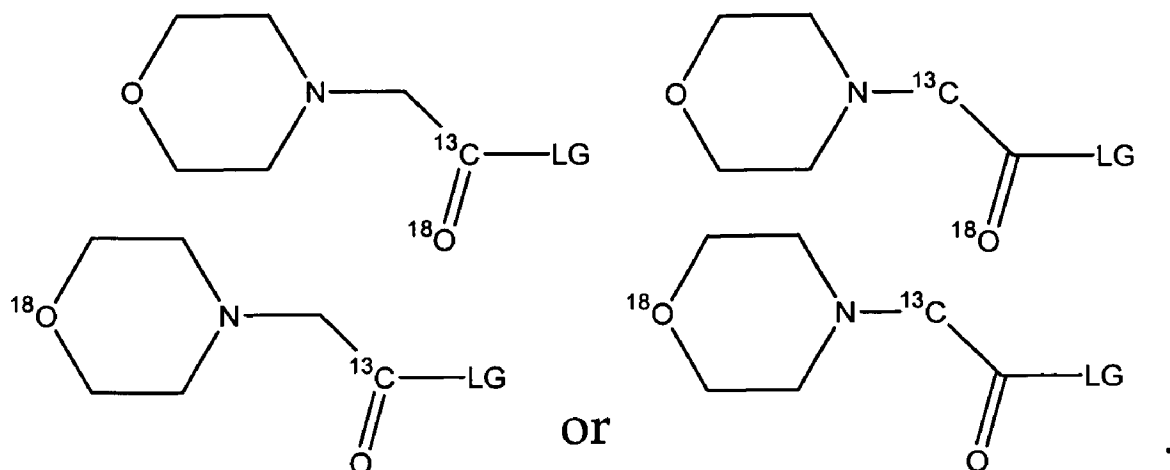
Request For Expedited Issuance of Certificate of Correction

Sir:

This Request For Expedited Issuance of Certificate of Correction in the above-identified patent is made pursuant to 37 C.F.R. 1.322. As the errors sought to be corrected are believed to have been incurred through the fault of the Office, Patentees request that this Request be expedited under MPEP 1480.01.

First Error

In Claim 12, each instance of "RG" should read --LG--, and the formulae should appear as follows:



Claim 12 was first presented as claim 73 on page 15 of the Office Action Response dated June 8, 2006 (attached hereto). (*See also*, Index of Claims (attached hereto)). This Response contained the correct formulae. (Office Action Response dated June 8, 2006, page 15). This Response was fully considered and claim 73 was allowed. (Notice of Allowability, page 1, number 2 and page 2, first and second paras. (attached hereto)). Thus, claim 73 (issued as claim 12) as presented by Patentees had the correct formula, and the publication of the above-identified patent with the incorrect formula is respectfully believed to be the fault of the Office.

Second Error

In claim 39, at column 52, line 2, the word "add" should read --acid--. Claim 39, which was originally filed as claim 42, was amended on page 21 of the Office Action Response dated December 19, 2005 (attached hereto). (*See also*, Index of Claims). This Response contained the correct word, --acid--. (Office Action Response dated December 19, 2005, page 21). This Response was entered; and the claim was later allowed. (Office Action mailed March 20, 2006 (attached hereto); Notice of Allowability, page

U.S. Patent No. 7,195,751
U.S. Application No.: 10/765,267
Compositions and Kits Pertaining to Analyte Determination
Atty Docket no.: 262_BP_0207_03_US

1, number 2). Thus, claim 42 (issued as claim 39) as presented by Patentees had the correct wording, and the publication of the above-identified patent with the incorrect wording is respectfully believed to be the fault of the Office.

Conclusion

Patentees respectfully request expedited issuance of a certificate of correction in the above-identified patent.

Patentees believe that no fees are due in connection with this paper or the accompanying Form PTO/SB/44. However, should any fees be due, any and all applicable fees may be charged to Deposit Account No. 50-4976.

Respectfully submitted,
Grasso PLLC



by: Fred Grasso
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February 25, 2011
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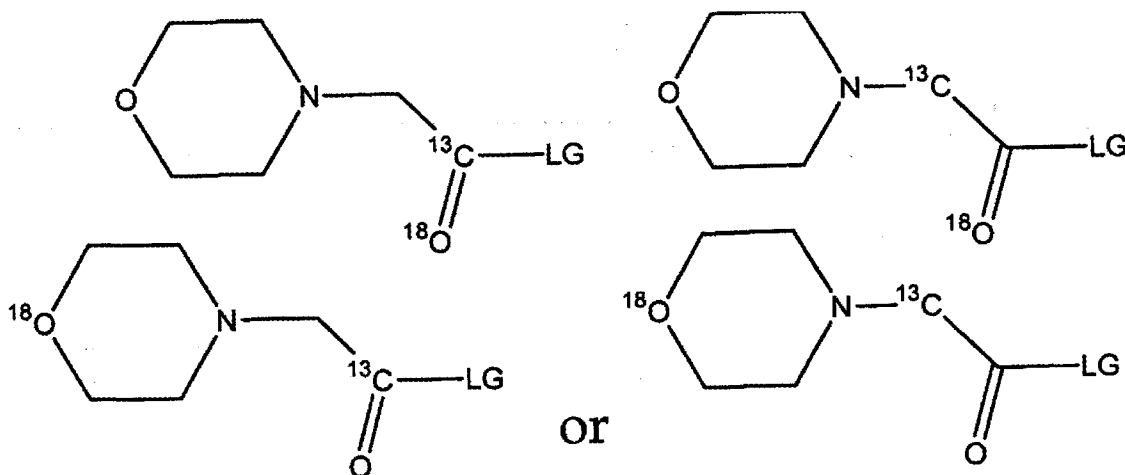
UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 7,195,751
APPLICATION NO.: 10/765,267
ISSUE DATE : March 27, 2007
INVENTOR(S) : Darryl J.C. Pappin; Michael Bartlet-Jones

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 48, lines 2-14, the four formulae should appear as follows:



Column 52, line 2, the word "add" should read --acid--.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Fred Grasso, Grasso PLLC
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This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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BP0207-US3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Serial No: 10/765,267 Confirmation No. 9577
Date Filed: January 27, 2004
Application Title: Compositions And Kits Pertaining To Analyte Determination
Applicants: Pappin et al.
Group Art Unit: 1626
Examiner: Nyeemah, Grazier
Action Type: Office Action – non-Final
Action Date: September 19, 2005

Certificate of Mailing Pursuant to:
37 C.F.R. § 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail No. ED 557927507 US in an Express Mail envelope addressed to: Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 19th day of December, 2005.

Brian D. Gildea
Reg. No. 39,995

OFFICE ACTION RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This response is being filed within the 3-month shortened statutory period set by the Office. Accordingly, please consider the following response to the Office Action mailed on September 19, 2005.

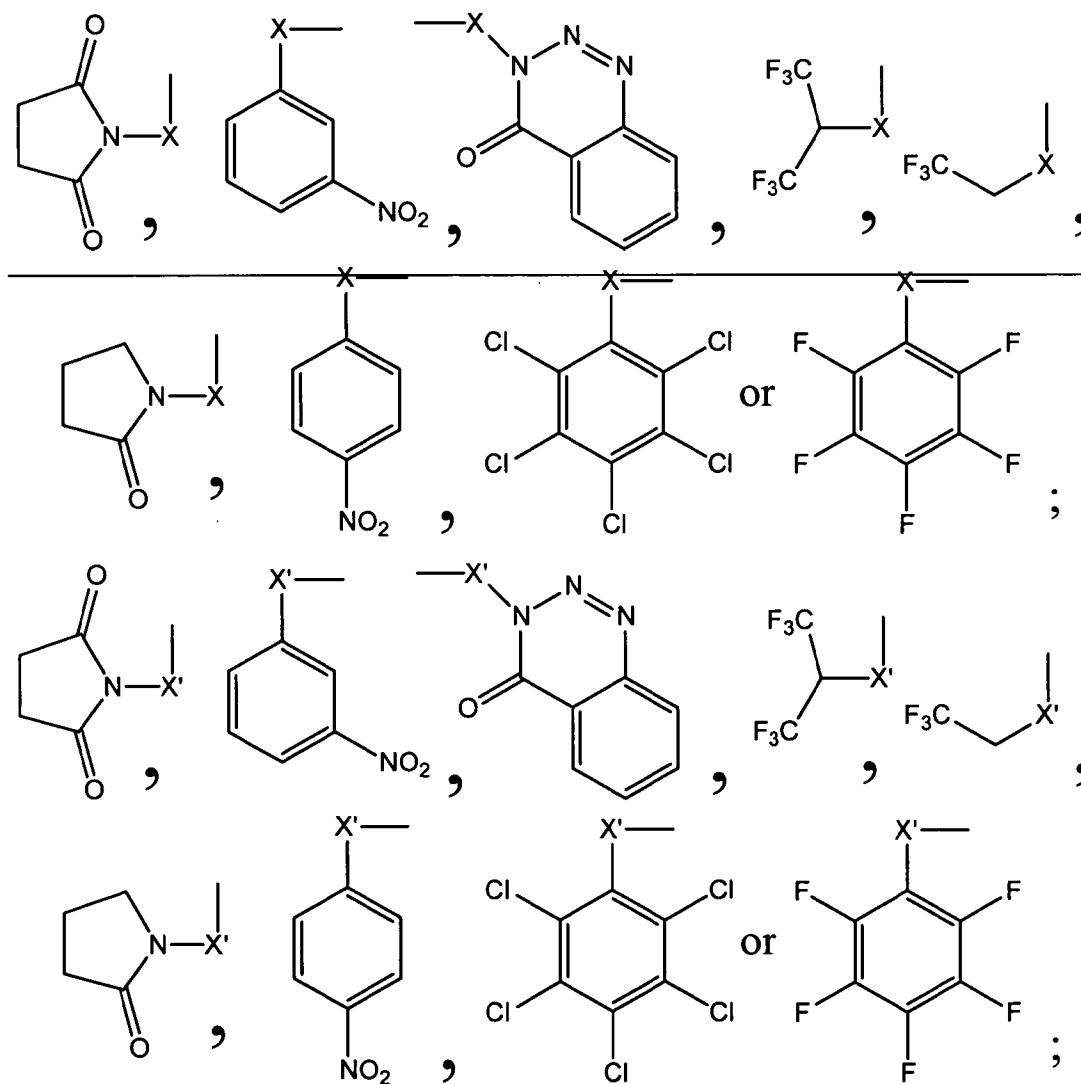
I. ACTION SUMMARY

Claims 1-70 stand pending in the application. Claims 54-70 stand withdrawn from consideration by the Examiner. Claims 1-15, 23, 28, 36 and 41-53 stand rejected. Claims 16-22, 24-27, 29-35, 37-40 and 42-53 stand objected to. No claim stands allowed.

II. AMENDMENT OF THE SPECIFICATION

Please amend the paragraph beginning on page 8, line 6 to page 9, line 2 as follows:

The reactive group of a labeling reagent can be an amine reactive group. For example the amine reactive group can be an active ester. Active esters are well known in peptide synthesis and refer to certain esters that are easily reacted with the N- α amine of an amino acid under conditions commonly used in peptide synthesis. The amine reactive active ester can be an N-hydroxysuccinimidyl ester, a N-hydroxysulfosuccinimidyl ester, a pentafluorophenyl ester, a 2-nitrophenyl ester, a 4-nitrophenyl ester, a 2,4-dinitrophenylester or a 2,4-dihalophenyl ester. For example, the alcohol or thiol group of an active ester can have the formula:



wherein X' is O or S, but preferably O. All of the foregoing being alcohol or thiol groups known to form active esters in the field of peptide chemistry wherein said alcohol or thiol group is displaced by the reaction of the N- α -amine of the amino acid with the carbonyl carbon of the ester. It should be apparent that the active ester (e.g. N-hydroxysuccinimidyl ester) of any suitable labelling/tagging reagent described herein could be prepared using well-known procedures (See: Greg T. Hermanson(1996). "The Chemistry of Reactive Groups" in "Bioconjugate Techniques" Chapter 2 pages 137-165, Academic Press, (New_York); also see: Innovation And Perspectives In Solid Phase Synthesis, Editor: Roger Epton, SPCC (UK) Ltd, Birmingham, 1990). Methods for the formation of active esters of N-substituted piperazine acetic acids compounds that are representative examples of labelling reagents of the general formula: RP-X-LK-Y-RG, are described in co-pending and commonly owned United States Patent Application Serial No. 10/751,354, incorporated herein by reference.

Please amend the paragraph at page 10, lines 15 to 28 as follows:

The reporter either comprises a fixed charge or is capable of becoming ionized. Because the reporter either comprises a fixed charge or is capable of being ionized, the labeling reagent might be isolated or used to label the reactive analyte in a salt or zwitterionic form. Ionization of the reporter facilitates its determination in a mass spectrometer. Accordingly, the reporter can be determined as an ion, sometimes referred to as a signature ion. When ionized, the reporter can comprise one or more net positive or negative charges. Thus, the reporter can comprise one or more acidic groups or basic groups since such groups can be easily ionized in a mass spectrometer. For example, the reporter can comprise one or more basic nitrogen atoms (positive charge) or one or more ionizable acidic groups such as a carboxylic acid group, sulfonic acid group or phosphoric acid group (negative charge). Non-limiting examples of reporters comprising a basic nitrogen include, substituted or unsubstituted, morpholines, piperidines or piperazines.

Please amend the paragraph at page 14, line 29 to page 15, line 6 as follows:

These types of mass spectrometers may be used in conjunction with a variety of ionization sources, including, but not limited to, electrospray ionization (ESI) and matrix-

assisted laser desorption ionization (MALDI). Ionization sources can be used to generate charged species for the first mass analysis where the analytes do not already possess a fixed charge. Additional mass spectrometry instruments and fragmentation methods include post-source decay in MALDI-MS instruments and high-energy CID using MALDI-TOF(time of flight)-TOF MS. For a recent review of tandem mass spectrometers please see: R. Aebersold and D. Goodlett, *Mass Spectrometry in Proteomics. Chem. Rev.* 101: 269-295 (2001). ~~Also see United States Patent No. 6,319,476, herein incorporated by reference, for a discussion of TOF-TOF mass analysis techniques.~~

Please amend the paragraph at page 16, lines 13-31 as follows:

In some embodiments, analytes can be determined based upon daughter-ion fragmentation patterns that are analyzed by computer-assisted comparison with the spectra of known or "theoretical" analytes. For example, the daughter fragment ion spectrum of a peptide ion fragmented under conditions of low energy CID can be considered the sum of many discrete fragmentation events. The common nomenclature differentiates daughter fragment ions according to the amide bond that breaks and the peptide fragment that retains charge following bond fission. Charge-retention on the N-terminal side of the fissile amide bond results in the formation of a b-type ion. If the charge remains on the C-terminal side of the broken amide bond, then the fragment ion is referred to as a y-type ion. In addition to b- and y-type ions, the CID mass spectrum may contain other diagnostic fragment ions (daughter fragment ions). These include ions generated by neutral loss of ammonia (-17 amu) from glutamine, lysine and arginine or the loss of water (-18 amu) from hydroxyl-containing amino acids such as serine and threonine. Certain amino acids have been observed to fragment more readily under conditions of low-energy CID than others. This is particularly apparent for peptides containing proline or aspartic acid residues, and even more so at aspartyl-proline bonds (Mak, M. et al., *Rapid Commun. Mass Spectrom.*, 12: 837-842) (1998). Accordingly, the peptide bond of a Z'-pro dimer or Z'-asp dimer, wherein Z' is any natural amino acid, pro is proline and asp is aspartic acid, will tend to be more labile as compared with the peptide bond between all other amino acid dimer combinations.

Please amend the paragraph at page 18, lines 8-16 as follows:

When the analyte of interest is a protein or peptide, the relative lability of bonds X and Y can be adjusted with regard to an amide (peptide) bond. Bond X, bond Y or both bonds X and Y can be more, equal or less labile as compared with a typical amide (peptide) bond. For example, under conditions of dissociative energy, bond X and/or bond Y can be less prone to fragmentation as compared with the peptide bond of a Z''-pro dimer or Z''-asp dimer, wherein Z'' is any natural amino acid, pro is proline and asp is aspartic acid. In some embodiments, bonds X and Y will fragment with approximately the same level of dissociative energy as a typical amide bond. In some embodiments, bonds X and Y will fragment at a greater level of dissociative energy as compared with a typical amide bond.

Please amend the paragraph at page 18, lines 8-16 as follows:

For example, the proteolytic enzyme trypsin is a serine protease that cleaves peptide bonds between lysine or arginine and an unspecific amino acid to thereby produce peptides that comprise an amine terminus (N-terminus) and lysine or arginine carboxyl terminal amino acid (C-terminus). In this way the peptides from the cleavage of the protein are predictable and their presence and/or quantity, in a sample from a trypsin digest, can be indicative of the presence and/or quantity of the protein of their origin. Moreover, the free amine termini of a peptide can be a good nucleophile that facilitates its labeling. Other exemplary proteolytic enzymes include papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin and carboxypeptid[e]ase C.

For example, a protein (e.g. protein Z''') might produce three peptides (e.g. peptides B, C and D) when digested with a protease such as trypsin. Accordingly, a sample that has been digested with a proteolytic enzyme, such as trypsin, and that when analyzed is confirmed to contain peptides B, C and D, can be said to have originally comprised the protein Z'''. The quantity of peptides B, C and D will also correlate with the quantity of protein Z''' in the sample that was digested. In this way, any determination of the identity and/or quantify of one or more of peptides B, C and D in a sample (or a fraction thereof), can be used to identify and/or quantify protein Z''' in the original sample (or a fraction thereof).

Please amend the paragraph at page 21, line 25 to page 22, line 6 as follows:

In some embodiments, the relative quantitation of differentially labeled identical analytes of a sample mixture is possible. Relative quantitation of differentially labeled identical analytes is possible by comparison of the relative amounts of reporter (e.g. area or height of the peak reported) that are determined in the second mass analysis for a selected, labeled analyte observed in a first mass analysis. Put differently, where each reporter can be correlated with information for a particular sample used to produce a sample mixture, the relative amount of that reporter, with respect to other reporters observed in the second mass analysis, is the relative amount of that analyte in the sample mixture. Where components combined to form the sample mixture is are known, the relative amount of the analyte in each sample used to prepare the sample mixture can be back calculated based upon the relative amounts of reporter observed for the ions of the labeled analyte selected from the first mass analysis. This process can be repeated for all of the different labeled analytes observed in the first mass analysis. In this way, the relative amount (often expressed in terms of concentration and/or quantity) of each reactive analyte, in each of the different samples used to produce the sample mixture, can be determined.

Please amend the paragraph at page 21, line 25 to page 22, line 6 as follows:

For example, the analyte might be a peptide that resulted from the degradation of a protein using an enzymatic digestion reaction to process the sample. Protein degradation can be accomplished by treatment of the sample with a proteolytic enzyme (e.g. trypsin, papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin or carboxypeptid[e]ase C). By determination of the identity and amount of a peptide in a sample mixture and identifying the sample from which it originated, optionally coupled with the determination of other peptides from that sample ~~sample~~, the precursor protein to the degraded peptide can be identified and/or quantified with respect to the sample from which it originated. Because this method allows for the multiplex determination of a protein, or proteins, in more than one sample (i.e. from a sample mixture), it is a multiplex method.

Please amend the paragraph at page 27, lines 1-8 as follows:

In some embodiments, the whole process can be repeated one or more times. For example, it may be useful to repeat the process one or more times where the sample mixture has been fractionated (e.g. separated by chromatography or electrophoresis). By repeating the process on each sample, it is possible to analyze all the entire sample mixture. It is contemplated that in some embodiments, the whole process will be repeated one or more times and within each of these repeats, certain steps will also be repeated one or more times such as described above. In this way, the contents of sample mixture can be interrogated and determined to the fullest possible extent.

Please amend the paragraph at page 37, lines 15-21 as follows:

In some embodiments, methods of the invention can further comprise digesting each sample with at least one enzyme to partially, or fully, degrade components of the sample prior to performing the labeling of the analytes of the sample (Also see the above section entitled: "Sample Processing"). For example, the enzyme can be a protease (to degrade proteins and peptides) or a nuclease (to degrade nucleic acids). The enzymes may also be used together to thereby degrade sample components. The enzyme can be a proteolytic enzyme such as trypsin, papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin or carboxypeptid[e]ase C.

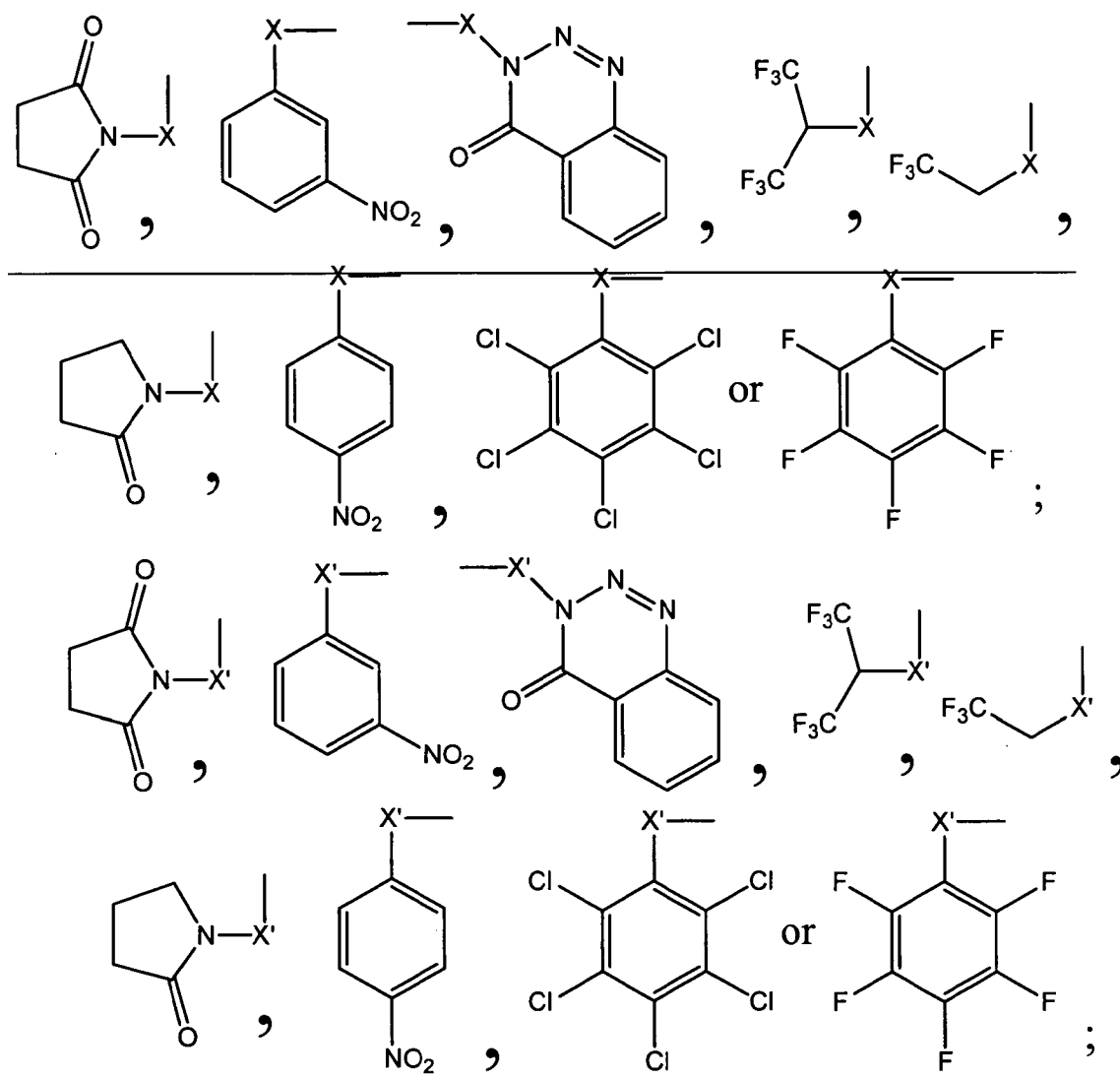
Please amend the paragraph at page 49, lines 3-6 as follows:

In some embodiments, the kit comprises a proteolytic enzyme. The proteolytic enzyme can be trypsin, papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin or carboxypeptid[e]ase C. In some embodiments, the kit can comprise instructions for using the labeling reagents to differentially label the analytes of different samples.

Please amend the paragraph at page 50, lines 12-17 as follows:

In some embodiments, the labeling reagents can comprise a carbonyl or thiocarbonyl linker. Labeling reagents comprising a carbonyl or thiocarbonyl linker can be used in active ester form for the labeling of analytes. In an active ester, an alcohol

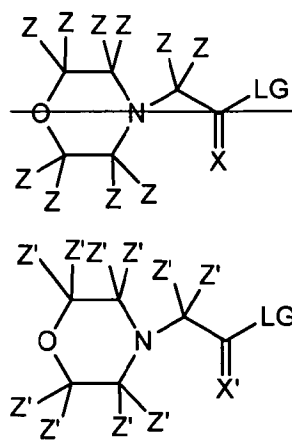
group forms a leaving group (LG). In some embodiments, the alcohol (LG) of the active ester can have the formula:



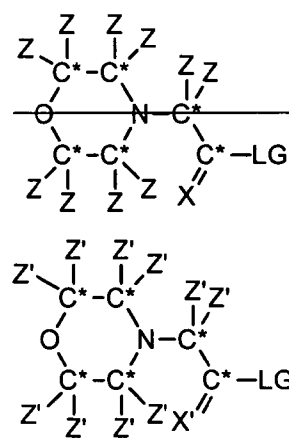
wherein X' is O or S. The active ester can be an N-hydroxysuccinimidyl ester.

Please amend the paragraphs at page 51, line 5 to page 53, line 14 as follows:

In some embodiments, the active ester compound can be an N-substituted morpholine acetic acid active ester compound of the formula:



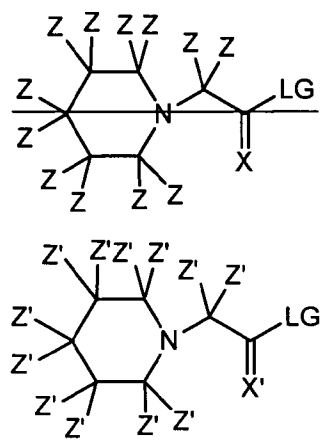
or a salt thereof, wherein; LG is the leaving group of an active ester; X' is O or S; each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms. In some embodiments, Z' independently can be hydrogen, deuterium, fluorine, chlorine, bromine or iodine. In some embodiments, Z' independently can be hydrogen, methyl or methoxy. In some embodiments, X' is ^{16}O or ^{18}O . The nitrogen atom of the morpholine ring can be ^{14}N or ^{15}N . In some embodiments, the active ester is a compound comprising the formula:



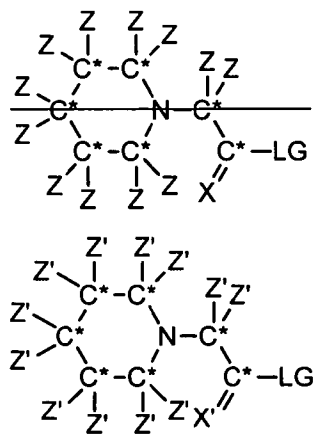
wherein each C^* is independently ^{12}C or ^{13}C ; LG is the leaving group of an active ester; X' is O or S; and each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon

atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

In some embodiments, the active ester compound can be an N-substituted piperidine acetic acid active ester compound of the formula:

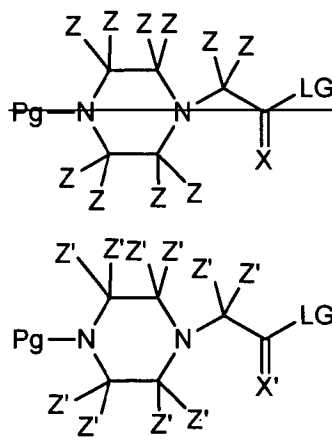


or a salt thereof, wherein; LG is the leaving group of an active ester; X₁ is O or S; each Z₁ is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms. In some embodiments, Z₁ independently can be hydrogen, deuterium, fluorine, chlorine, bromine or iodine. In some embodiments, Z₁ independently can be hydrogen, methyl or methoxy. In some embodiments X₁ is ¹⁶O or ¹⁸O. The nitrogen atom of the piperidine ring can be ¹⁴N or ¹⁵N. In some embodiments, the active ester is a compound comprising the formula:

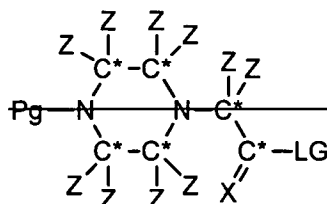


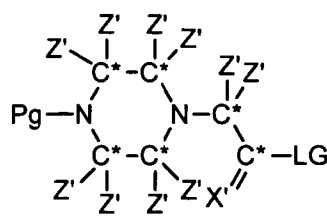
wherein each C* is independently ^{12}C or ^{13}C ; LG is the leaving group of an active ester; X' is O or S; and each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

In some embodiments, the active ester compound can be an N-substituted piperidine acetic acid active ester compound of the formula:



or a salt thereof, wherein; LG is the leaving group of an active ester; X' is O or S; Pg is an amine protecting group; and each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms. In some embodiments, Z' independently can be hydrogen, deuterium, fluorine, chlorine, bromine or iodine. In some embodiments, Z' independently can be hydrogen, methyl or methoxy. In some embodiments X' is ^{16}O or ^{18}O . In some embodiments, each nitrogen atom of the piperazine ring is ^{14}N or ^{15}N . In some embodiments, the active ester is a compound comprising the formula:





wherein each C* is independently ^{12}C or ^{13}C ; LG is the leaving group of an active ester; X' is O or S; Pg is an amine protecting group and each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

III. AMENDMENT OF THE CLAIMS

PLEASE ENTER THE FOLLOWING AMENDMENT WITHOUT PREJUDICE OR DISCLAIMER. Applicants reserve the right to file a divisional or continuation application to the originally filed claims.

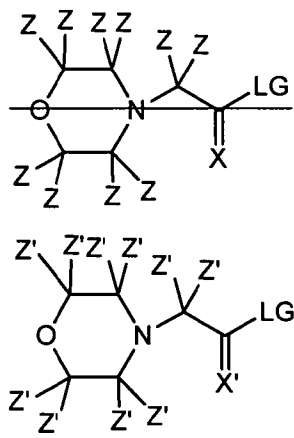
Claim 1 (Canceled)

2. (Currently Amended) The compound of claim 71, wherein the compound is isotopically enriched with three or more heavy atom isotopes.
3. (Currently Amended) The compound of claim 71, wherein the six-membered heterocyclic ring is substituted with one or more substituents.
4. (Original) The compound of claim 3, wherein the one or more substituents are alkyl, alkoxy or aryl groups.
5. (Original) The compound of claim 4, wherein the one or more substituents are protected or unprotected amine groups, hydroxyl groups or thiol groups.

Claims 6-7 (Canceled)

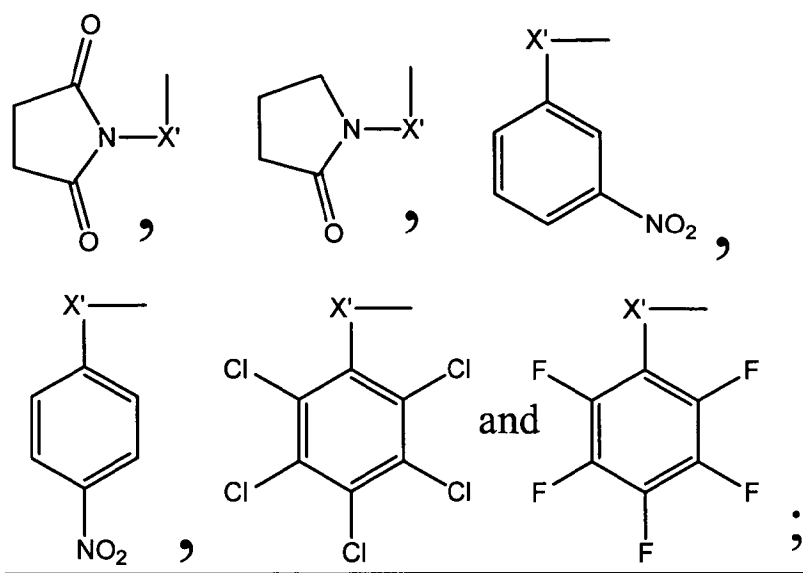
8. (Currently Amended) The compound of claim 71, wherein the six-membered heterocyclic ring comprises one or more additional nitrogen, oxygen or sulfur atoms.
9. (Currently Amended) The compound of claim 71, wherein ~~active ester is an N-hydroxysuccinimide ester~~ LG is N-hydroxysuccinimide.
10. (Currently Amended) The compound of claim 71, wherein the compound is a salt.

11. (Currently Amended) The compound of claim 71, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.
12. (Currently Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
13. (Currently Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 93 percent isotopic purity.
14. (Currently Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 96 percent isotopic purity.
15. (Currently Amended) An N-substituted morpholine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester selected from the group consisting of:



X' is O or S;

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms;
and

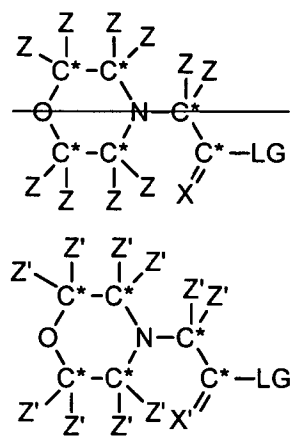
wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

16. (Original) The compound of claim 15, wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 17 (Canceled)

18. (Currently Amended) The compound of claim 15, wherein LG is N-hydroxysuccinimide.
19. (Currently Amended) The compound of claim 15, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

20. (Currently Amended) The compound of claim 15, wherein each $Z'_$ is independently hydrogen, methyl or methoxy.
21. (Currently Amended) The compound of claim 15, wherein $X'_$ is ^{16}O or ^{18}O .
22. (Original) The compound of claim 15, wherein the nitrogen atom of the morpholine ring is ^{14}N or ^{15}N .
23. (Currently Amended) The compound of claim 15, of the formula:



wherein;

each C^* is independently ^{12}C or ^{13}C ;

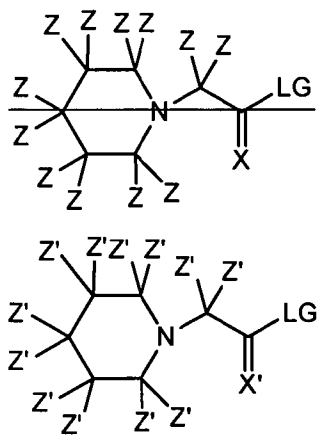
LG is the leaving group of an active ester as defined in claim 15;

$X'_$ is O or S ; and

each $Z'_$ is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

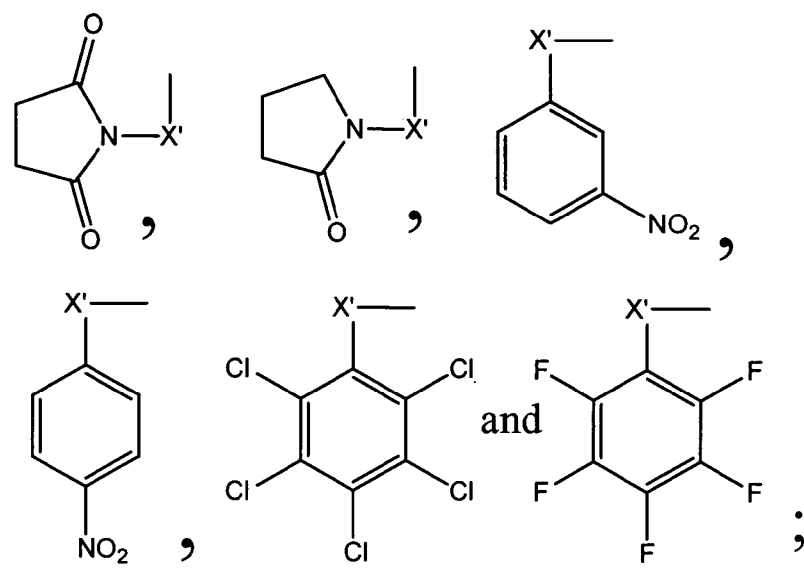
24. (Original) The compound of claim 15, wherein the compound is a mono-TFA salt or a mono-HCl salt.

25. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
26. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
27. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.
28. (Currently Amended) An N-substituted piperidine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester selected from the group consisting of:



X' is O or S;

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms;
and

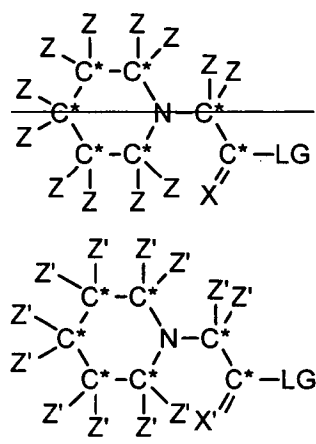
wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

29. (Original) The compound of claim 28, wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 30 (Canceled)

31. (Original) The compound of claim 28, wherein LG is N-hydroxysuccinimide.
32. (Currently Amended) The compound of claim 28, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

33. (Currently Amended) The compound of claim 28, wherein each $Z'_$ is independently hydrogen, methyl or methoxy.
34. (Currently Amended) The compound of claim 28, wherein $X'_$ is ^{16}O or ^{18}O .
35. (Original) The compound of claim 28, wherein the nitrogen atom of the piperidine ring is ^{14}N or ^{15}N .
36. (Currently Amended) The compound of claim 28, of the formula:



wherein;

each C^* is independently ^{12}C or ^{13}C ;

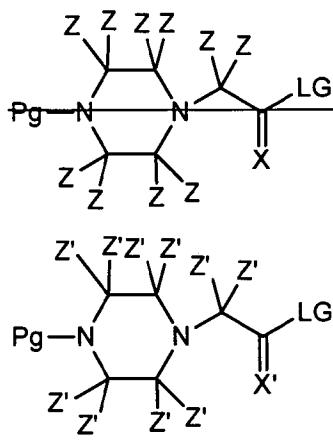
LG is the leaving group of an active ester as defined in claim 28;

$X'_$ is O or S; and

each $Z'_$ is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

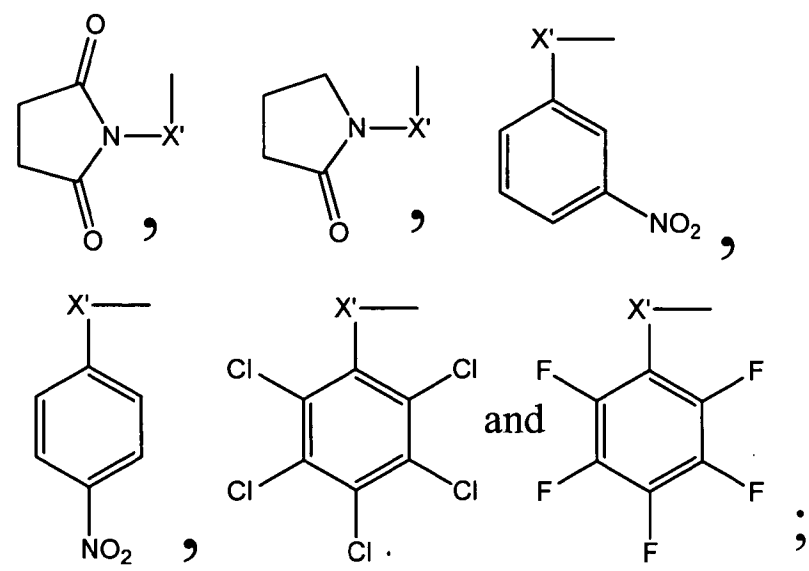
37. (Original) The compound of claim 28, wherein the compound is a mono-TFA salt or a mono-HCl salt.

38. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
39. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
40. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.
41. (Currently Amended) An N-substituted piperazine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester selected from the group consisting of:



X' is O or S;

Pg is an amine-protecting group;

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

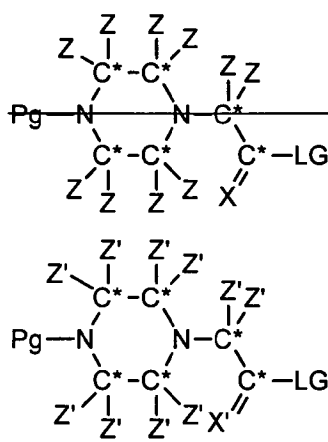
wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

42. (Currently Amended) The compound of claim 41, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 43 (Canceled)

44. (Original) The compound of claim 41, wherein LG is N-hydroxysuccinimide.
45. (Currently Amended) The compound of claim 41, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

46. (Currently Amended) The compound of claim 41, wherein each Z' is independently hydrogen, methyl or methoxy.
47. (Currently Amended) The compound of claim 41, wherein X' is ¹⁶O or ¹⁸O.
48. (Original) The compound of claim 41, wherein each nitrogen atom of the piperazine ring is ¹⁴N or ¹⁵N.
49. (Currently Amended) The compound of claim 41, of the formula:



wherein,

each C^* is independently ^{12}C or ^{13}C ;

LG is the leaving group of an active ester as defined in claim 41;

X' is O or S;

Pg is an amine protecting group; and

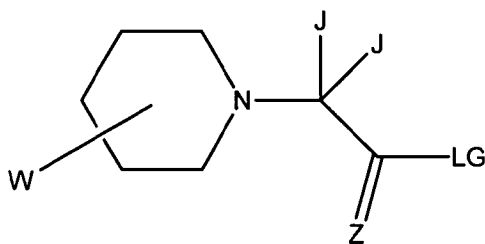
each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

50. (Currently Amended) The compound of claim 41, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.

51. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
52. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
53. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.

Claims 54-70 (Canceled)

71. (New) A compound of formula:



wherein,

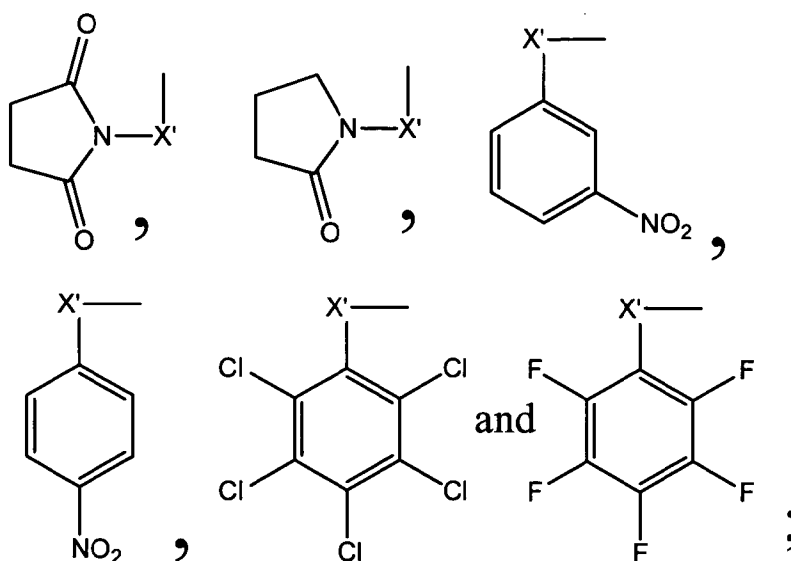
each carbon of the heterocyclic ring has the formula CJ_2 ;

W is an atom or group that is located ortho, meta or para to the ring nitrogen and is NH, N- R^1 , N- R^2 , P- R^1 , P- R^2 , O or S;

each J is the same or different and is H, deuterium (D), R^1 , OR^1 , SR^1 , NHR^1 , $N(R^1)_2$, fluorine, chlorine, bromine or iodine;

Z is O, S, NH or NR^1 ; and

LG is an alcohol or thiol leaving group selected from the group consisting of:



wherein,

X' is O or S;

R¹ is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms; and

R² is an amino alkyl, hydroxy alkyl, thio alkyl group or a cleavable linker that cleavably links the reagent to a solid support wherein the amino alkyl, hydroxy alkyl or thio alkyl group comprises one to eight carbon atoms, which may optionally contain a heteroatom or a substituted or unsubstituted aryl group, and wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms; and

wherein the compound is isotopically enriched with one or more heavy atom isotopes.

72. (New) A method comprising:

- reacting an analyte with the compound of claim 71 to thereby produce a labeled analyte; and
- mixing the labeled analyte with one or more differentially labeled analytes.

IV. REMARKS ON THE AMENDMENTS

Remarks on the Amendment to the Specification:

Various paragraphs were amended to correct clerical errors. For example several paragraphs were amended to correct the spelling of carboxypeptidase to carboxypeptidase. In these cases, brackets [] were used to indicate deletion of the "e" since a strikethrough "e" is not easily perceived. (See 37 C.F.R. § 1.121(b)(1)(ii) for the use of brackets)

Various other paragraphs were amended to avoid confusion where the same variable was used differently. For example, X was used in some cases to mean "O or S" and in other cases X (i.e. in the structure "RP-X-LK-Y-RG") was used to signify a bond. Where X was intended to mean "O or S", X is now X'. Similarly, Z was used in various paragraphs. As appropriate, Z', Z'' and Z''' are now also used for clarity.

An amendment to the text of page 14 is requested since it has been determined that the patent identified was incorrectly referenced.

Remarks on the Amendment to the claims:

Claims 54-70 are canceled in response to the restriction requirement.

Claim 71 is newly presented as a substitute to claim 1 as per discussions occurring on December 8, 2005 at the interview discussed below. Antecedent basis for this amendment can be found throughout the specification but in particular at page 45, line 21 to page 46, line 2 and page 49, line 8 to page 53, line 14.

Claim 72 is presented as a new method claim that includes all the compound limitations of claim 71. Because it includes all the compound limitations of claim 71, it is believed that claim 72 can be properly rejoined under *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q.2d 1127 (Fed Cir. 1995) even if the Office determines that restriction is proper. Antecedent basis for claim 72 can be found throughout the specification but in particular at page 23, line 26 to page 25, line 32.

The amendments to other claims have been made to, *inter alia*, correct for dependencies, correct for punctuation and make the claims consistent with amendments to the specification (i.e. change X to X' and Z to Z', Z'' or Z'''). Other amendments are made to clarify the claim language.

It is believed that no new matter has been added.

V. FORMAL MATTERS

1. Interview

The Examiner (Nyeemah Grazier) and her supervisor (Dr. Kamal Saeed) are thanked for the courtesy extended to Applicant's representative during the interview on December 8, 2005. Comments contained in this submission memorialize those discussions. (See: 37 C.F.R. § 1.133)

2. Information Disclosure Statements

Return of the signed PTO-1449 forms filed on August 5, 2004 and December 27, 2004 is acknowledged. The Examiner is thanked for return of these documents. Review of these documents revealed that two of the references were not considered. Reference EP 990047 B1 (Ref. BO) is resubmitted for review in a new Information Disclosure Statement discussed below. The corresponding US Patent application (US 2005-0049406 A1 - in English) related to WO03/040288 (Ref. BL) is also submitted in the new Information Disclosure Statement. Additional references are also submitted for review. The Examiner is requested to review these references and return the PTO-1449 with the next Office correspondence.

3. New Information Disclosure Statement

As discussed above, two references are resubmitted for consideration in a new IDS. One or more additional references may also be presented. Review of these documents and return of the executed PTO-1449 with the next Office communication is respectfully requested.

VI. RESTRICTION REQUIREMENT

In response to the telephone request by Examiner Grazier on September 8, 2005, attorney Gildea did make a provisional election, **with traverse**, of Group I, claims 1-53. Because an election of a particular species was required in response to the restriction

requirement (37 U.S.C. §1.146), compound I in Figure 1A was provisionally elected as a species of the claimed genus (e.g. see claim 1).

At pages 2-9 of the present Office Action, the rationale supporting the restriction requirement is set forth. As articulated, the restriction requirement appears to be based upon a two-tier analysis. First, claims 1-70 are restricted into two groups of claims (i.e. Group I, claims 1-53 and Group II, claims 54-70) and then, the election of species is used as a basis to further limit the subject matter within specific claims by way of an objection, finally articulated at page 16 (i.e. the second tier). At the second tier (i.e. restriction within specific claims) the argument seems to imply that improper Markush grouping has been used (OA at page 3). Regardless, restriction is asserted as being proper under 35 U.S.C. § 121. (*Id.*). Applicants respectfully traverse the restriction requirement, in part, for the following reasons.

Applicants do not traverse the restriction between Groups I and II. Accordingly, claims 54-70 are canceled in the amendment set forth above.

However, Applicants do traverse the remainder of the restriction requirement. Specifically, Applicants challenge all assertions that either the claims contain improper Markush grouping or that restriction under 35 U.S.C. 121 can properly be used to require Applicants to amend individual claims to thereby cancel non-elected subject matter. As will be discussed in more detail below, it is respectfully submitted that the decisions in *In re Weber* and *In re Haas* prohibit such action by the Office. While it is noted that the cancellation of claim 1 coupled with the submission of new claim 71 may render moot certain aspects of the argument presented below, this argument is intended to address the full scope of the restriction requirement so that Applicants may preserve their right to petition for reconsideration of the entire scope of restriction requirement. (See: 37 C.F.R. § 1.144 or 1.181)

In *Weber*, the court reasoned that if the Office could restrict subject matter within a single claim, such claims would never be examined on their merits. *In re Weber*, 580 F.2d 455, 458, 198 U.S.P.Q. 328, 331 (CCPA, 1978) Consequently, *Weber* holds that:

“It is apparent that § 121 provides the Commissioner with the authority to promulgate rules designed to Restrict an Application to one of several claimed inventions when those inventions are found to be “independent and distinct”. It

does not, however, provide a basis to an examiner acting under the authority of the Commissioner to Reject a particular Claim on that same basis."

(*In re Weber*, 580 F.2d 455, 458, 198 U.S.P.Q. 328, 331-332 (CCPA, 1978))

"We hold that a rejection under § 121 violates the basic right of the applicant to claim his invention as he chooses." (emphasis added).

(*Weber* at 459, 198 U.S.P.Q. at 332 (CCPA, 1978))

Accordingly, it is clear from *In re Weber* that the legal issue of whether or not the Office may impose a restriction requirement and thereby refuse to examine subject matter within the scope of a single claim so restricted has been decided against the Office. It is well settled that such requirements violate 35 U.S.C. § 112, where the applicant is statutorily entitled to claim his invention as he deems proper, notwithstanding 35 U.S.C. § 121. **This is true whether or not the single claim comprises two or more independent and distinct inventions.**

At page 3 of the Office Action, it is asserted that restriction of a Markush group is proper where the compounds within the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. Citation is made to *In re Harnisch* 631 F.2d 716, 206 USPQ 300 (CCPA) and *Ex Parte Hozumi*, 3 USPQ2d 1059 (BPAI 1984). While *In re Harnisch* acknowledged that restriction within a single claim could be required where a Markush group lacks unity of invention, it is respectfully submitted that the Office Action fails to establish that improper Markush grouping is present in claims 1-53.

As a preliminary matter, Applicants note that claim 1 is a generic claim and does not use Markush format. Moreover, the Office Action properly recites that *"Absent evidence that subject matter of the Markush-type claim lacks unity of invention, the Office may not merely refuse to examine that which applicants regard as their invention."* (OA at page 3) Reference is also made to page 8 of the Office Action wherein the Examiner acknowledges that under the practice sanctioned in MPEP 803.02, which addresses the possibility of multiple inventions within a single claim, examiners are instructed to first examine the elected invention and if it is determined to be patentable and then to continue the search and examine other subject matter within that claim to determine

whether the subject matter in the claim, as a whole, is patentable. M.P.E.P § 803.02. Moreover, the mandate of M.P.E.P. 803.02 does not sanction the required amendment of single claims except where prior art is found that would prohibit that allowability of a Markush type claim, as drafted. Because no 35 U.S.C. § 102 or 35 U.S.C. § 103 rejections have been articulated in the present action, it seems that M.P.E.P § 803.02 mandates that the entirety of the claimed subject matter be searched unless prior art is found that would require an amendment of the claimed subject matter.

Notwithstanding these facts, the present Office Action states: *“Claims 1-17, 19-30, 32-43, 45-53 are objected to as containing non-elected subject matter. To overcome this objection, Applicant should rewrite instant Claims in independent form including all of the limitations of the base claim and any intervening claims and if rewritten directed solely to the elected subject matter indicated as being examinable.”* (emphasis added in underlined text, OA at page 16). For the reasons stated, it is believed that such an rejection, and related objection, is improper, and indeed conflicts with the decisions in *Weber*, 580 F.2d 455, 198 U.S.P.Q. 328 (CCPA, 1978), *Haas* 198 USPQ 334 (CCPA, 1978) as well as *Harnisch*, 631 F.2d 716, 722, 206 U.S.P.Q. 300, 305 (CCPA, 1980). Reconsideration of the restriction requirement and withdrawal of the rejection and above cited “objection” is respectfully requested.

While it is noted that at page 8, the Office Action asserts that *“... the compounds are withdrawn as being non-elected subject matter that differs materially in structure and composition”* (OA at page 8) it is believed that the claimed subject matter possesses a “common utility” and thereby possesses “unity of invention”. *Id.* at 722, 206 U.S.P.Q. at 305. In the present case, it is respectfully submitted that the specification clearly states that the compositions can all be used as labeling reagents (i.e. the common function) for multiplex analysis of one or more analytes in the same sample, or in two or more different samples (Specification at page 49, lines 8-15). Moreover, the structure of these compounds is fixed as an active ester compound that is a 5, 6 or 7 membered heterocyclic ring comprising a ring nitrogen atom that is N-alkylated with a substituted or unsubstituted acetic acid moiety to which the alcohol moiety of the active ester is linked through the carbonyl carbon of the N-alkyl acetic acid moiety (i.e. the single structural similarity), wherein the compound is isotopically enriched with one or more heavy atom isotopes (Specification at page 50, lines 18-23 and claim 1). Because the present claims

comply with the requirements of unity of invention as articulated in *Harnisch*, it is believed that they recite a proper Markush group.

Because the restriction requirement is yet to be made final, no petition for review under 37 C.F.R. § 1.144 can be filed. Moreover, it is believed that the amendment offered by Applicants eliminates many of the concerns articulated by the Examiner and her supervisor in during the interview on December 8, 2005. However, to the extent that the Office maintains that further restriction and amendment of claim 71 is proper, Applicants traverse such action for the reasons stated above.

VII. RESPONSE TO THE OFFICE ACTION REJECTIONS

1. Rejection For Obviousness-Type Double Patenting

As discussed during the interview on December 8, 2005, since both patent applications remain pending, claims of one or both applications can be amended and/or canceled. Accordingly, this provisional rejection should be held in abeyance until such time as both patent applications contain allowable subject matter or in the alternative until this application is determined to have otherwise allowable subject matter. At such time, Applicants can reconsider the requirement for a terminal disclaimer.

2. Rejection Under 35 U.S.C. § 112, first paragraph

Section 2163 of the M.P.E.P (which addresses rejections under 35 U.S.C. § 112, first paragraph) states: "*A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption.*" (M.P.E.P § 2163.04). "*The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description.*" (*Id.*) "*The absence of definitions or details for well-established terms or procedures should not be the basis for a rejection under 35 U.S.C. § 112, para. 1, for lack of written description.*" (M.P.E.P. § 2163(II)(A)(1)) For example, the well-established term "nail" need not be defined in a patent pertaining to an article of manufacture unless the Applicant intends that the term to mean something other than its well-established definition (e.g. for the term "nail" to also mean "staple").

At page 15, the Office Action asserts that: "*The variable "PG" in claims 41 and 49 is not defined in the Specification sufficiently to ascertain the structure of the protection group.*" However, according to the M.P.E.P § 2163(II)(A)(1), the specification need not define or

provide details for a well-established term. Consequently, evidence that "amine protecting group" is a well-established term precludes the appropriateness of the asserted rejection particularly since the application is presumed to be adequate as filed.

According to the specification, "*PG is an amine protecting group*" (Specification at page 52, lines 20-21). The specification also refers to Green et al., *Protecting Groups In Organic Synthesis*, Third Edition, John Wiley & Sons, Inc. New York, 1999 as a reference source for examples of amine, hydroxyl and thiol groups (Specification at page 35, lines 23-26). Pages 494-653 of the Green et al. reference describes examples of amine protecting groups commonly used in organic synthesis. These pages, which are submitted in the new IDS filed with this Office Action response, are evidence that "amine protecting group" is a well-established term of art of organic chemistry. Therefore, it need not be defined or commented on in detail in the specification.

Other evidence that "amine protecting group" is a well-established term can be found by searching just the claims of patents searchable on the United States Patent & Trademark Office website (www.uspto.gov). The results of a search performed on November 30, 2005 (Attached as Exhibit A-1) revealed 186 US Patents containing "amine protecting group" as a claim term. A definition for "protecting group" obtained from the *Dictionary of Biochemistry and Molecular Biology*, Second Edition, John Wiley & Sons, Inc. New York, 1989 is also submitted as Exhibit A-2. From this definition and the structure at page 52, it is self evident that an amine protecting group would be any protecting group that protects the illustrated amine group of the heterocyclic ring. Taken together, it is respectfully submitted that the evidence demonstrates that "amine protecting group" is a well-established term.

While it is noted that the Examiner's supervisor (Examiner Kamal Saeed) argued at the interview of December 8, 2005 that in his experience some patent applicants will defined "protecting group" in their specifications to include groups (for example hydrogen) not typically considered by the ordinary practitioner to be a protecting group, it is respectfully submitted that such argument is irrelevant and off point. An applicant can be his own lexicographer. M.P.E.P. § 2173.01. In fact, it is imperative that an applicant define a term or phrase where he intends it to have other than its common meaning else his claim containing said term or phrase will not be interpreted as he

intends. While those definitions provided by an applicant in his specification (i.e. Applicant acting as his own lexicographer) are appropriate for understanding the scope of the claims of his application (i.e. where applicant is his own lexicographer), they are irrelevant to the interpretation of all other patent applications such as the present application. This is obvious because, as stated in the M.P.E.P sections quoted above, there is no requirement that the specification define well-established terms where Applicant intends to avail himself/herself of that common meaning. Since the evidence demonstrates that “amine protecting group” is well-established in the organic chemistry art, such as “nail” is well-established in the article of manufacture art, the assertion that Applicants must define “amine protecting group” is clearly erroneous.

Accordingly, it is submitted that the rejection under 35 U.S.C. 112, first paragraph for use of “PG” in claims 41 and 49 is inappropriate in view of the evidence. In fact, the Examiner has submitted no evidence whatsoever suggesting that “amine protecting group” is not well-established. Thus, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

3. Rejection Under 35 U.S.C. § 112, second paragraph

At page 15 of the Office Action, claims 41-53 are rejected as being indefinite for the reasons stated in the 35 U.S.C. § 112, first paragraph rejection. For the reasons stated above, it is believed that “PG” is defined in Applicant’s specification using a well-established term (i.e. amine protecting group). Therefore, it is submitted that claims 41-53 comply with 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

At page 15 of the Office Action, claims 1, 15, 23, 28, 36, 41 and 49 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite because the claims represent an “omnibus type claim”. Omnibus (adjective) is defined in the Merriam-Webster OnLine Dictionary (www.m-w.com) as 1) of, relating to, or providing for many things at once; and 2) containing or including many items (see attached Exhibit B). It seems that by this characterization, the Examiner is asserting that the claims are broad in scope.

According to M.P.E.P. § 2173.04, *“Breath of a claim is not equated with indefiniteness”*. Accordingly, it is respectfully submitted that the assertion claims 1, 15, 23, 28, 36, 41 and

49 are indefinite because they "include many items" (i.e. are broad) is not recognized as a valid rejection. Regardless, claim 1 has been canceled and new claim 71 presented for examination. Moreover, claims 15, 23, 28, 36 and 41 have been amended.

Reconsideration and withdrawal of the rejection is respectfully requested.

At page 15-16, bridging paragraph, the Office Action suggests that claim terms such as "heterocyclic ring", "active ester", "leaving group" and "amine protecting group" need to be defined in light of the scope of the elected subject matter. For reasons previously argued, it is believed that the restriction requirement is flawed and that the objection set forth on page 16 should be withdrawn. It is also respectfully submitted that these are well-established terms. Definitions and other evidence of the use of these well-established terms in the claims of issued US patents are presented in Exhibits A-1, A-2, C-1, C-2, D-1, D-2, E-1 and E-2 (attached). With respect to the terms "active ester" and "leaving group", further reference is also made to the specification at page 8, line 6 to page 9, line 2 as well as to page 50, lines 12 to 16. Regardless, claim 1 has been canceled and new claim 71 presented for examination. Moreover, claims 15, 23, 28, 36 and 41 have been amended. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

VIII. SUMMARY

It is believed that this response addresses all rejections set forth in the present Office Action and the application is in ready condition for allowance. In consideration of the preceding amendments and remarks, Applicants hereby respectfully request reconsideration of all pending claims, the withdrawal of all rejections set forth in the present Office Action and issue of a Notice of Allowance by The Office.

IX. INTERVIEW

If the Examiner believes a telephonic or personal interview would advance the prosecution of the subject application, the Examiner is invited to contact attorney Gildea during business hours at the telephone or facsimile numbers listed below.

X. FEES

A new IDS and authorization to deduct the appropriate fee from Deposit Account 01-2213 for consideration of said IDS is being submitted herewith. Because the amendment set forth herein does not increase the claim count beyond that already on record, it is believed that there is no requirement for the payment of any additional fee. Because this response is being filed within the shorted statutory period for response, again it is believed that no fee is required for consideration of this response by the Office. If however, The Office determines that any fee is properly due for its consideration of this paper, authorization is hereby granted to charge any required fee associated with the filing or proper consideration of this paper to Deposit Account 01-2213 (Invoice No. BP0207-US3).

XI. CORRESPONDENCE/CUSTOMER NUMBER

Please send all correspondence pertaining to this document to:

Brian D. Gildea, Esq.
Applied Biosystems
500 Old Connecticut Path
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IF NOT ALREADY DONE, PLEASE ASSOCIATE THIS CASE WITH CUSTOMER NUMBER

23544

Respectfully submitted
on behalf of Applicants,

Dec 19, 2005
Date

Brian D. Gildea
Brian D. Gildea, Esq.; Reg. No. 39,995



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,267	01/27/2004	Darryl J.C. Pappin	BP0207-US 3	9577
23544	7590	03/20/2006	EXAMINER	
APPLIED BIOSYSTEMS 500 OLD CONNECTICUT PATH FRAMINGHAM, MA 01701			GRAZIER, NYEEMAH	
			ART UNIT	PAPER NUMBER
			1626	
DATE MAILED: 03/20/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/765,267	Applicant(s) PAPPIN ET AL.	
	Examiner Nyeemah Grazier	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-5, 8-16, 18-29, 31-42, 44-53, 71 and 72 is/are pending in the application.
- 4a) Of the above claim(s) 72 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 3, 4, 8, 10, 11, 15, 20, 33, 41, 42, 44-53 and 71 is/are rejected.
- 7) ☒ Claim(s) 2, 5, 9, 12-14, 16, 18, 19 and 21-27 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/20/05, 12/09/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

I. ACTION SUMMARY

Claims 2-5, 8-16, 18-29, 31-42, 44-53, 71 and 72 are currently pending. Claim 1, 6-7, 17, 30, 43, and 54-70 are cancelled. Claim 71 is newly added and hereby withdrawn as not being drawn to the elected invention, namely compounds. Claim 72 is withdrawn as being drawn to a non-elected invention. 37 C.F.R. § 1.142(b).

II. INFORMATION DISCLOSURE STATEMENT

The supplemental information disclosure statements (IDS) submitted on January 20, 2006 and December 19, 2005 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner. The supplemental IDS submitted on January 20, 2006 is not in compliance with 37 CFR 1.98 because dates for references with citation number HF and HG do not have dates. Please provide date for these references.

III. RESTRICTION/ELECTION

A. Response to Formal Matters

Applicant's election with traverse of Group (I), originally claims 1-53, drawn to compounds and compositions, in the reply filed on December 19, 2005 is acknowledged. Applicant has submitted Amendments to the Claims on December 19, 2005. The elected

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invention reads on claims 2-5, 8-16, 18-29, 31-42, 44-53, and 71. The traversal is on the ground(s) that the restriction with in Group (I), is improper under 35 M.P.E.P. §803.02. (See Remarks, pp. 27-29). This is not found persuasive because as stated in the Actions, the inventions of Group (I), namely, claim 1 (now cancelled) are independent and distinct.

The election of specie requirement was a *provisional election for search purposes*. Alternatively the compounds and compositions of group (I) present a burden because the compounds are independent and distinct. For example, a 7 membered heterocyclic rings containing at least one nitrogen are classified in the U.S. Classification System in class 540, while a 6 membered heterocyclic rings containing at least one nitrogen and one or more heteroatoms are classified in class 544 and other six membered heterocyclic rings containing one nitrogen are classified in 546. Five memebered rings containing at least one nitrogen are classified in class 548. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. The requirement is still deemed proper and is therefore made FINAL.

B. Response to Arguments

1. Obviousness-Type Rejection

Applicant's arguments, see Remarks, filed on December 19, 2005, with respect to the provisional double patenting rejection have been fully considered. In view of the amendments to

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the claims filed on December 19, 2005, claims 2-14 depend from new claim 71, which is drawn to a morpholine and not a piperazine. Thus the rejection of claims 2-14 have been obviated.

However, applicants arguments pertaining to the obviousness rejection of claims 41-53 is not persuasive and is therefore maintained. To obviate this rejection, the applicant should submit a terminal disclaimer.

2. 35 U.S.C. 112,1st Rejection

Applicant's arguments, see Remarks, filed on December 19, 2005, with respect to 35 U.S.C. 112 rejection with respect to claims 41 and 49 have been fully considered and are persuasive. The rejection is withdrawn.

3. 35 U.S.C. 112,2nd Rejection

Applicant's arguments, see Remarks, filed on December 19, 2005, with respect to 35 U.S.C. 112, 2nd rejection with respect to claims 41-53 and 1, 15, 23, 28, 36, 41 and 49 have been fully considered. Upon further consideration of the claim amendments, the rejections have been obviated.

IV. REJECTION(S)

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. Claim 71 states "each carbon of the heterocyclic ring has the formula CJ_2 ." However, the definition of J_2 is neither disclosed in the Specification nor the claim. The variable J_2 is unclear because J_2 may be an independent variable or maybe Applicant means to say $C(J)_2$.

Claims 3 and 4 recite the limitation "one or more substituent" in reference to substitution on the piperidine ring of claim 71. There is insufficient antecedent basis for this limitation in the claim because the structure appears to be drawn to a piperidine ring with one substitution, namely "W." Claim 71 states that each carbon member of the ring has the formula CJ_2 , but " J_2 " is ambiguous as it has not been defined and it is undetermined whether applicant intend $C(J)_2$.

Claim 10 recites the limitation "wherein the compound is a salt." There is insufficient antecedent basis for the abovementioned limitation because claim 71 is not drawn to a salt form.

Claim 8 recites the limitation "wherein the six member heterocyclic ring comprises one or more additional nitrogen, oxygen or sulfur atom." There is insufficient antecedent basis for the abovementioned limitation because claim 8 depends from claim 71 and claim 71 is drawn to a piperidine ring.

Claim 11 recites the limitation “ wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt” There is insufficient antecedent basis for the abovementioned limitation because claim 71 is not drawn to a salt form.

Claims 20, 33 and 46 recite the limitation “methoxy.” There is insufficient antecedent basis for the abovementioned limitation because the claims from which the rejected claims depend (*i.e.* 15, 28 and 41, respectively) do not recite methoxy as a definition for z’.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by *Banasiak, et al.*, (EP 209763 A1). The *Banasiak, et al.* reference discloses 2, 6-dimethyl, 4-nitrophenyl morpholinacetic acid. (See, Attachment A, Accession No. 1987:156487 HCAPLUS). The reference anticipates the instant invention wherein x’ is oxygen, LG is 4-nitrophenyl, and where z’ (ortho to the oxygen atom on the morpholine ring) are CH₃ and the other is hydrogen.

Claims 41, 44 and 46 are rejected as being anticipated by *Sawayama, et al.*, (JP 01125357 A2). (See, Attachment B, Accession No. 1990:7937 HCAPLUS). The *Sawayama, et al.*

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reference anticipates the instant invention where x' is oxygen, z' is methyl at the N-linked carbon), LG is 2,5-pyrrolidinedione and where Pg is a benzyl group.

V. ALLOWABLE SUBJECT MATTER

The allowable subject matter includes the compounds and compositions of claims 28, 29, 31-32, 34-40.

VI. OBJECTION(S)

Dependent Claim Objections

Dependent Claims 2-14, 16, 18-27, 42, and 44-53 are also objected to as being dependent upon a rejected based claim. To overcome this objection and assuming the dependent claim is not rejected, Applicant should rewrite said claims in an independent form and include the limitations of the base claim and any intervening claim.

VII. CONCLUSION

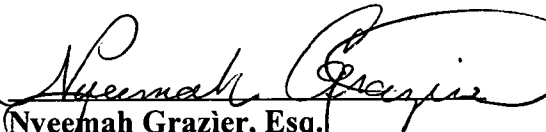
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,


Nyeemah Grazier, Esq.
Patent Examiner, Art Unit 1626
UNITED STATES PATENT AND TRADEMARK OFFICE
400 Dulany Street
Alexandria, VA 22314-5774
Tel. No.: (571) 272-8781

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER


for **Joseph K. McKane**
Supervisory Primary Examiner, Art Unit 1626
UNITED STATES PATENT AND TRADEMARK OFFICE
400 Dulany Street
Alexandria, VA 22314-5774
Tel. No.: (571) 272-0699

ATTACHMENT A

ATTACHMENT B



06-09-06

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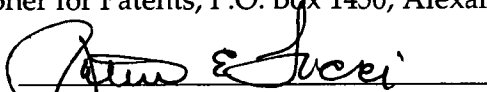
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Serial No: 10/765,267 Confirmation No. 9577
Date Filed: January 27, 2004
Application Title: Compositions And Kits Pertaining To Analyte Determination
Applicants: Pappin et al.
Group Art Unit: 1626
Examiner: Nyeemah, Grazier
Action Type: Office Action – non-Final
Action Date: March 20, 2006

Certificate of Mailing Pursuant to:
37 C.F.R. § 1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail No. ED 557927555 US in an Express Mail envelope addressed to: Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 8th day of June 2006.


Patricia E. Tocci

OFFICE ACTION RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

This response is being filed within the 3-month shortened statutory period set by the Office. Accordingly, please consider the following response to the Office Action mailed on March 20, 2006.

I. ACTION SUMMARY

Claims 2-5, 8-16, 18-29, 31-42, 44-53, 71 and 72 stand pending in the application. Claim 72 stands withdrawn from consideration by the Examiner. Claims 3, 4, 8, 10, 11, 15, 20, 33, 41, 42, 44-53 and 71 stand rejected. Claims 2, 5, 9, 12-14, 16, 18, 19 and 21-27 stand objected to. Claims 28, 29, 31, 32 and 34-40 appear to be allowed (See page 7 of the Office Action) but the Office Action Summary suggests that no claim stands allowed.

II. AMENDMENT

A. In the Specification:

Upon review of the amendment submitted on December 19, 2005 it has been observed that two conflicting instructions were included on page 5 and similarly on page 6. In particular, on page 5, two instructions were requested to “... *amend the paragraph at page 18, lines 8-16 as follows.*” It is respectfully submitted that the second instruction should have read as follows.

Please amend the paragraph at page 19, lines 10-26 as follows:

For example, the proteolytic enzyme trypsin is a serine protease that cleaves peptide bonds between lysine or arginine and an unspecific amino acid to thereby produce peptides that comprise an amine terminus (N-terminus) and lysine or arginine carboxyl terminal amino acid (C-terminus). In this way the peptides from the cleavage of the protein are predictable and their presence and/or quantity, in a sample from a trypsin digest, can be indicative of the presence and/or quantity of the protein of their origin. Moreover, the free amine termini of a peptide can be a good nucleophile that facilitates its labeling. Other exemplary proteolytic enzymes include papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin and carboxypeptid[e]ase C.

For example, a protein (e.g. protein Z'') might produce three peptides (e.g. peptides B, C and D) when digested with a protease such as trypsin. Accordingly, a sample that has been digested with a proteolytic enzyme, such as trypsin, and that when analyzed is confirmed to contain peptides B, C and D, can be said to have originally comprised the protein Z''. The quantity of peptides B, C and D will also correlate with the quantity of protein Z'' in the sample that was digested. In this way, any determination of the identity and/or quantify of one or more of peptides B, C and D in a sample (or a fraction thereof), can be used to identify and/or quantify protein Z'' in the original sample (or a fraction thereof).

Similarly, on page 6, two instructions were requested to “... *amend the paragraph at page 21, line 25 to page 22, line 6 as follows:* It is respectfully submitted that the second instruction should have read as follows.

Please amend the paragraph at page 24, lines 22-31 as follows:

For example, the analyte might be a peptide that resulted from the degradation of a protein using an enzymatic digestion reaction to process the sample. Protein degradation can be accomplished by treatment of the sample with a proteolytic enzyme (e.g. trypsin, papain, pepsin, ArgC, LysC, V8 protease, AspN, pronase, chymotrypsin or carboxypeptid[e]ase C). By determination of the identity and amount of a peptide in a sample mixture and identifying the sample from which it originated, optionally coupled with the determination of other peptides from that sample ~~sample~~, the precursor protein to the degraded peptide can be identified and/or quantified with respect to the sample from which it originated. Because this method allows for the multiplex determination of a protein, or proteins, in more than one sample (i.e. from a sample mixture), it is a multiplex method.

Accordingly, it is requested that the specification be amended as indicated and that the faulty instructions at pages 5 and 6 of the response dated December 19, 2006 be disregarded.

B. In the Claims:

PLEASE ENTER THE FOLLOWING AMENDMENT WITHOUT PREJUDICE OR DISCLAIMER. Applicants reserve the right to file a divisional or continuation application to the originally filed claims.

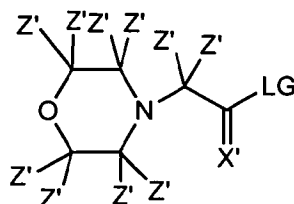
Claim 1 (Canceled)

2. (Previously Amended) The compound of claim 71, wherein the compound is isotopically enriched with three or more heavy atom isotopes.
3. (Previously Amended) The compound of claim 71, wherein the six-membered heterocyclic ring is substituted with one or more substituents.
4. (Original) The compound of claim 3, wherein the one or more substituents are alkyl, alkoxy or aryl groups.

Claims 5-7 (Canceled)

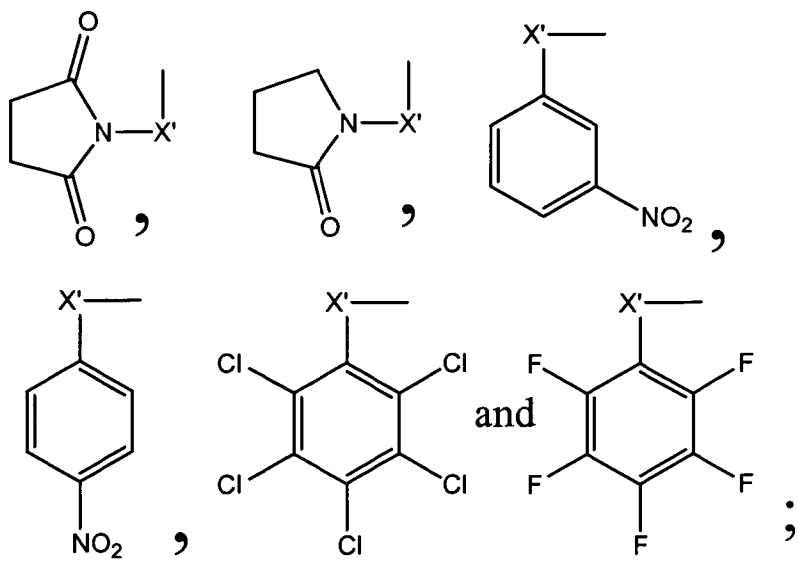
8. (Previously Amended) The compound of claim 71, wherein the six-membered heterocyclic ring comprises one or more additional nitrogen, oxygen or sulfur atoms.
9. (Previously Amended) The compound of claim 71, wherein LG is N-hydroxysuccinimide.
10. (Previously Amended) The compound of claim 71, wherein the compound is a salt.
11. (Previously Amended) The compound of claim 71, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.

12. (Previously Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
13. (Previously Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 93 percent isotopic purity.
14. (Previously Amended) The compound of claim 71, wherein each incorporated heavy atom isotope is present in at least 96 percent isotopic purity.
15. (Previously Amended) An N-substituted morpholine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester selected from the group consisting of:



X' is O or S;

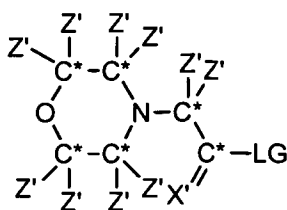
each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

16. (Original) The compound of claim 15, wherein the N-substituted morpholine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 17 (Canceled)

18. (Original) The compound of claim 15, wherein LG is N-hydroxysuccinimide.
19. (Previously Amended) The compound of claim 15, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.
20. (Currently Amended) The compound of claim 15, wherein each Z' is independently hydrogen, or methyl ~~or methoxy~~.
21. (Previously Amended) The compound of claim 15, wherein X' is ^{16}O or ^{18}O .
22. (Original) The compound of claim 15, wherein the nitrogen atom of the morpholine ring is ^{14}N or ^{15}N .
23. (Previously Amended) The compound of claim 15, of the formula:



wherein;

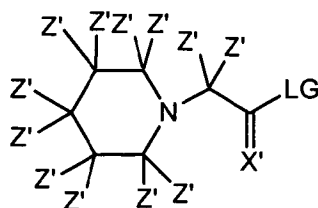
each C* is independently ^{12}C or ^{13}C ;

LG is the leaving group of an active ester as defined in claim 15;

X' is O or S; and

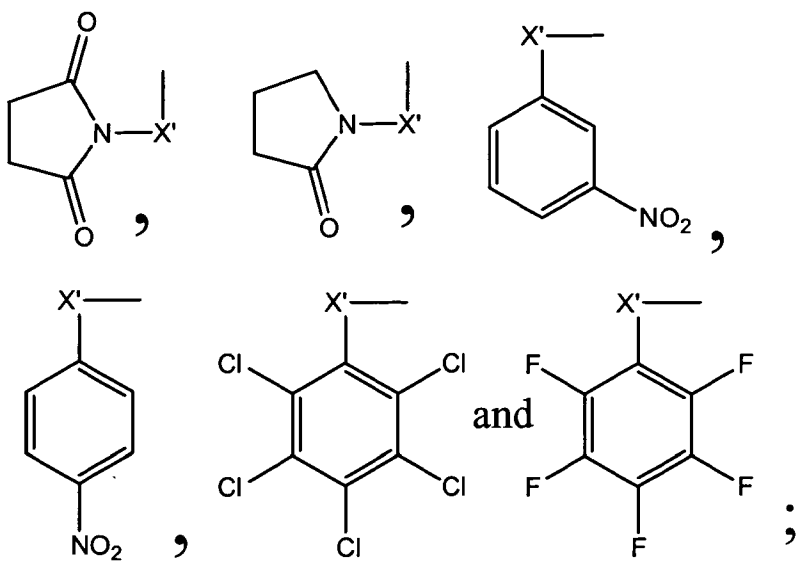
each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

24. (Original) The compound of claim 15, wherein the compound is a mono-TFA salt or a mono-HCl salt.
25. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
26. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
27. (Original) The compound of claim 15, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.
28. (Previously Amended) An N-substituted piperidine acetic acid active ester compound of the formula:



or a salt thereof, wherein;

LG is the leaving group of an active ester selected from the group consisting of:



X' is O or S;

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms;

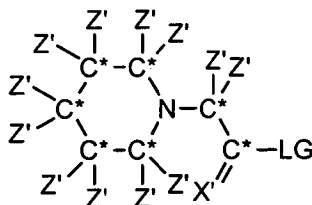
and

wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

29. (Original) The compound of claim 28, wherein the N-substituted piperidine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 30 (Canceled)

31. (Original) The compound of claim 28, wherein LG is N-hydroxysuccinimide.
32. (Previously Amended) The compound of claim 28, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.
33. (Currently Amended) The compound of claim 28, wherein each Z' is independently hydrogen, or methyl ~~or methoxy~~.
34. (Previously Amended) The compound of claim 28, wherein X' is ^{16}O or ^{18}O .
35. (Original) The compound of claim 28, wherein the nitrogen atom of the piperidine ring is ^{14}N or ^{15}N .
36. (Previously Amended) The compound of claim 28, of the formula:



wherein;

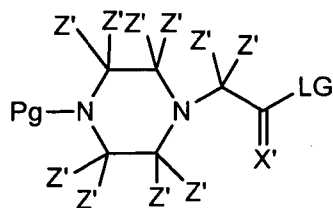
each C* is independently ^{12}C or ^{13}C ;

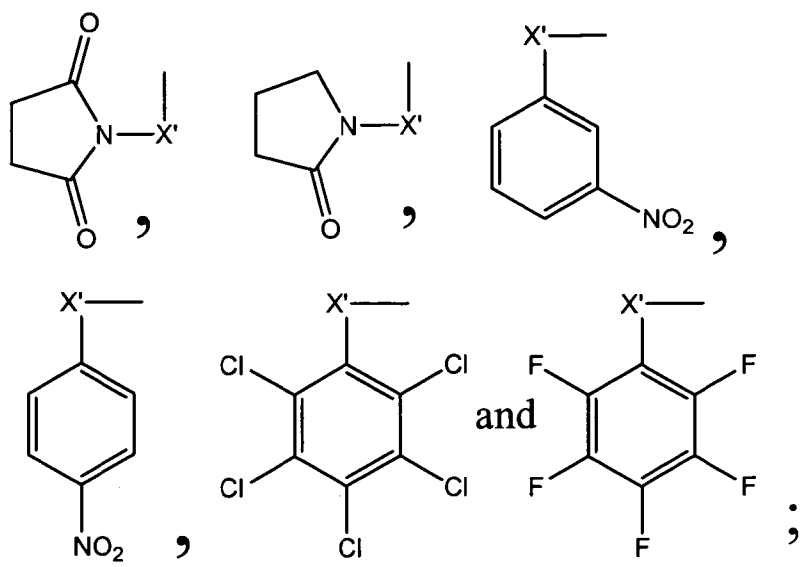
LG is the leaving group of an active ester as defined in claim 28;

X' is O or S; and

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.

37. (Original) The compound of claim 28, wherein the compound is a mono-TFA salt or a mono-HCl salt.
38. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.
39. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
40. (Original) The compound of claim 28, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.
41. (Previously Amended) An N-substituted piperazine acetic acid active ester compound of the formula:





X' is O or S;

Pg is an amine-protecting group;

each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms; and

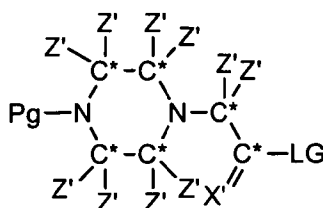
wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with one or more heavy atom isotopes.

42. (Previously Amended) The compound of claim 41, wherein the N-substituted piperazine acetic acid active ester is isotopically enriched with three or more heavy atom isotopes.

Claim 43 (Canceled)

44. (Original) The compound of claim 41, wherein LG is N-hydroxysuccinimide.
45. (Previously Amended) The compound of claim 41, wherein each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine or iodine.

46. (Currently Amended) The compound of claim 41, wherein each Z' is independently hydrogen, or methyl or methoxy.
47. (Previously Amended) The compound of claim 41, wherein X' is ^{16}O or ^{18}O .
48. (Original) The compound of claim 41, wherein each nitrogen atom of the piperazine ring is ^{14}N or ^{15}N .
49. (Previously Amended) The compound of claim 41, of the formula:



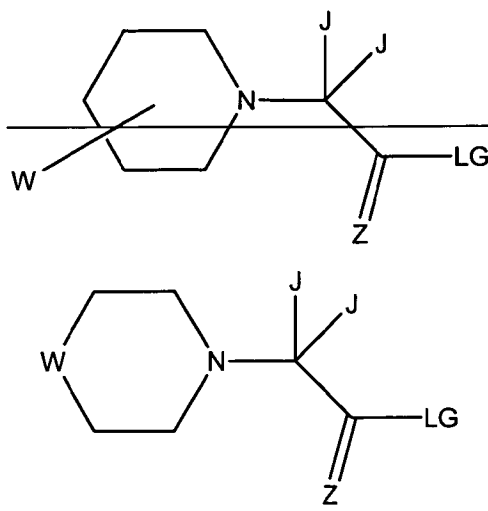
wherein,

- each C* is independently ^{12}C or ^{13}C ;
 - LG is the leaving group of an active ester as defined in claim 41;
 - X' is O or S;
 - Pg is an amine protecting group; and
 - each Z' is independently hydrogen, deuterium, fluorine, chlorine, bromine, iodine, an amino acid side chain or a straight chain or branched C1-C6 alkyl group that may optionally contain a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups each independently comprise linked hydrogen, deuterium or fluorine atoms.
50. (Previously Amended) The compound of claim 41, wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.
51. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 80 percent isotopic purity.

52. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 93 percent or isotopic purity.
53. (Original) The compound of claim 41, wherein each incorporated heavy atom isotope is present in at least 96 percent or isotopic purity.

Claims 54-70 (Canceled)

71. (Currently Amended) A compound of formula:



or a salt thereof, wherein,

each carbon of the heterocyclic ring has the formula $C(J)_2$;

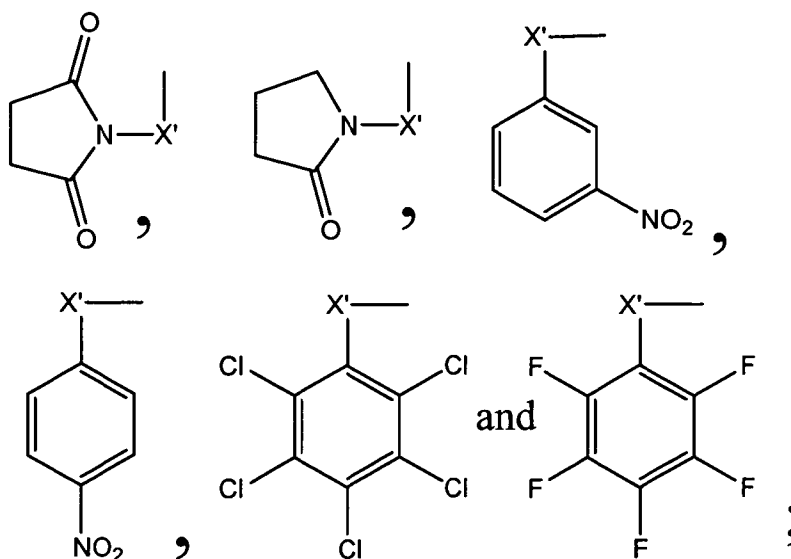
~~W is an atom or group that is located ortho, meta or para to the ring nitrogen~~
and is NH , $N-R^1$, $N-R^2$, $P-R^1$, $P-R^2$, $O-C$ or S ;

each J is the same or different and is H , deuterium (D), R^1 , OR^1 , SR^1 , NHR^1 ,

$N(R^1)_2$, fluorine, chlorine, bromine or iodine;

Z is O , S , NH or NR^1 ; and

LG is an alcohol or thiol leaving group selected from the group consisting of:



wherein,

X' is O or S;

R¹ is the same or different and is an alkyl group comprising one to eight carbon atoms which may optionally contain a heteroatom or a substituted or unsubstituted aryl group wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms; and

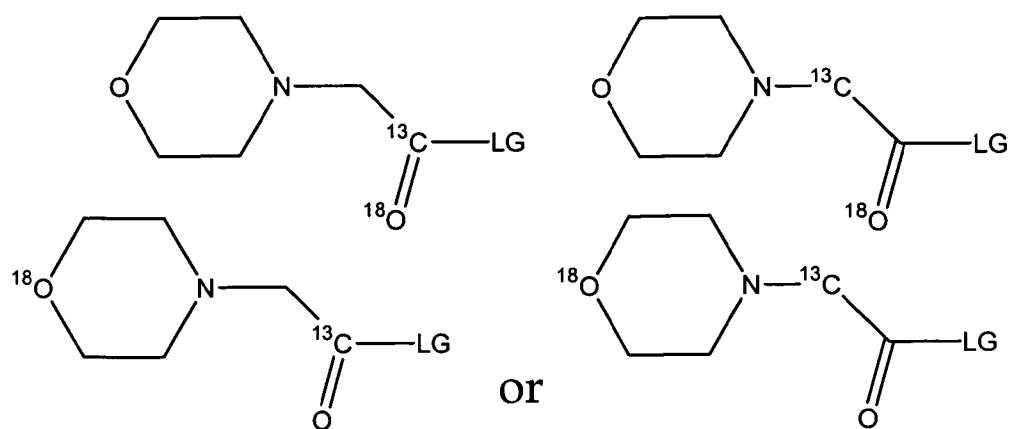
R² is an amino alkyl, hydroxy alkyl, thio alkyl group or a cleavable linker that cleavably links the reagent to a solid support wherein the amino alkyl, hydroxy alkyl or thio alkyl group comprises one to eight carbon atoms, which may optionally contain a heteroatom or a substituted or unsubstituted aryl group, and wherein the carbon atoms of the alkyl and aryl groups independently comprise linked hydrogen, deuterium and/or fluorine atoms; and

wherein the compound is isotopically enriched with one or more heavy atom isotopes.

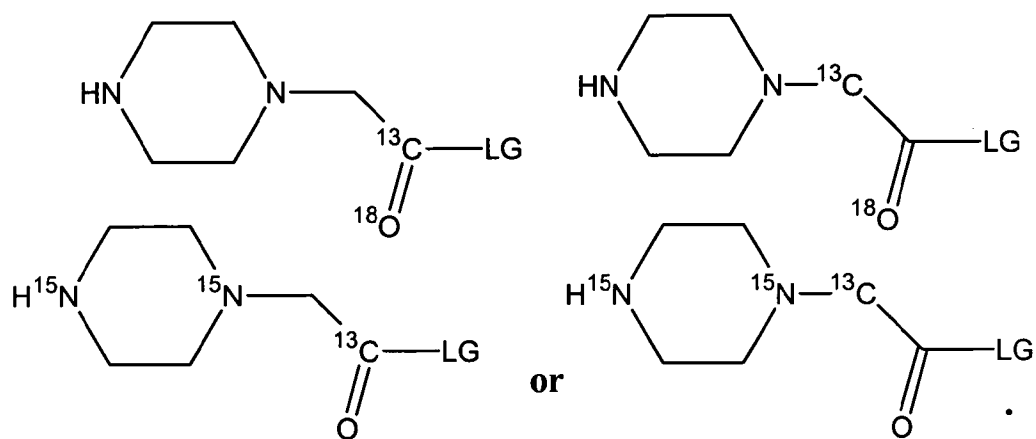
72. (Previously Presented, Withdrawn) A method comprising:

- a) reacting an analyte with the compound of claim 71 to thereby produce a labeled analyte; and
- b) mixing the labeled analyte with one or more differentially labeled analytes.

73. (New) The compound of claim 71 of the formula:



74. (New) The compound of claim 71 of the formula:



III. REMARKS ON THE AMENDMENTS

Remarks on the Amendment to the Specification

As stated above, the requested amendment mirrors that previously made on pages 5 and 6 of Applicants' response dated December 19, 2005 but wherein the requested paragraphs were incorrectly identified. Entry of the amendments at page 19, lines 10-26 and page 24, lines 22-31 is requested. Moreover, it is requested that the prior incorrect second set of instructions at pages 5 and 6 of Applicants' response of December 19, 2005 be disregarded.

It is believed that no new matter is added by entry of this amendment.

Remarks on the Amendment to the Claims:

The characterization of claim 18 has been corrected. In the amendment filed on December 19, 2005, claim 18 was characterized as "Currently Amended" but no amendment was presented. Upon review, it seems that Claim 18, as presently presented, is Original and has been so characterized.

Claims 20, 33 and 46 are amended to address the concern articulated by the Examiner in paragraph IV of the Office Action.

Claim 71 has been amended to include salt forms of the compound. Antecedent basis for this amendment can be found throughout the specification but in particular at page 50, lines 3-11. The claim has also been amended as suggested by the Examiner at page 5 of the Office Action and as discussed during the personal interview on May 25, 2006.

New claims 73-74 are added to more distinctly claim the subject matter for which Applicants seek a patent. Antecedent basis for these claims can be found throughout the specification but in particular at page 45, line 22 to page 47, line 12.

It is believed that no new matter is added by entry of this amendment.

IV. FORMAL MATTERS

1. Interview

The Examiner (Nyeemah Grazier) and her supervisor (Dr. Kamal Saeed) are thanked for the courtesy extended to Applicants' representative during the interview on May 25, 2006. Comments contained in this submission are intended to be additive to those set forth in the Interview Summary prepared by Examiner Riley on May 25, 2006. (See: 37 C.F.R. § 1.133)

2. Status of Certain Claims

At paragraph I (page 2) of the Office Action, there is a remark suggesting that claim 71 is withdrawn because it does not relate to a compound. Respectfully, claim 71 is drawn to a compound. Moreover, the remainder of the Office Action suggests that claim 71 is pending, including the Office Action Summary. The pendency of claim 71 was confirmed during the personal interview on May 25, 2006. The Examiner is requested to confirm this fact in the next communication from the Office.

According to the Office Action Summary, no claims appear to be allowed. However, according to page 7 of the Office Action, it appears that claims 28, 29, 31-32 and 34-40 are allowed. Clarification is requested. That claims 28, 29, 31-32 and 34-40 are allowed was confirmed during the personal interview on May 25, 2006. The Examiner is requested to confirm this fact in the next communication from the Office.

3. New Information Disclosure Statement

At paragraph II (page 2) of the present Office Action, the Examiner notes that no dates are entered for references HF and HG. Said references are resubmitted with an IDS accompanying this response wherein the dates of publication are identified in PTO-1449. Additionally, an English translation of EP 209763A1 and JP 01125357 (both cited by the Examiner at page 6 of the present Office Action) is submitted. One or more additional references may also be presented. Review of these documents and return of the executed PTO-1449 with the next Office communication is respectfully requested. Authorization to deduct the appropriate fee for consideration of these references can be found in the papers that accompany this response.

4. Restriction Requirement

It is acknowledged that the restriction requirement was deemed proper and made FINAL according to pages 2-3 of the Office Action. Although Applicants disagree that restriction is proper (at least for the reasons argued in Applicants' response dated December 19, 2005), it is believed that amendments previously entered render moot substantially all of the issues raised by the original restriction requirement. Accordingly, Applicants reserve the right to petition for reconsideration (under 37 C.F.R. § 1.144) of the restriction requirement. Nevertheless, because it seems that Applicants' prior amendments have rendered moot the controversy, Applicants will await a Final Action before deciding whether or not to file said petition.

5. Other Co-Pending Applications Owned by Applera Corporation

For the convenience of the Examiner, reference is made to the following copending applications owned by Applera Corporation. The Examiner is invited to review the claims of these applications for consideration of any other obviousness type double patenting rejections that he/she may feel is appropriate.

Title	Serial No.	Filing Date
Active Esters of N-Substituted Piperazine Acetic Acids, Including Isotopically Enriched Versions Thereof	10/751,354	05 Jan 2004
Isotopically Enriched N-Substituted Piperazine Acetic Acids And Methods For The Preparation Thereof	10/751,387	05 Jan 2004
Isotopically Enriched N-Substituted Piperazines And Methods For The Preparation Thereof	10/751,388	05 Jan 2004
Methods And Mixtures Pertaining To Analyte Determination Using Electrophilic Labeling Reagents	10/765,264	27 Jan 2004
Compositions And Kits Pertaining To Analyte Determination	10/765,267	27 Jan 2004
Methods And Mixtures Pertaining To Analyte Determination	10/765,458	27 Jan 2004
Mixtures Of Isobarically Labeled Analytes And Fragments Ions Derived Therefrom	10/822,639	12 Apr 2004
Isobarically Labeled Analytes And Fragment Ions Derived Therefrom	10/852,730	24 May 2004
Method And Apparatus For De-Convoluting A Convolved Spectrum	10/916,629	12 Aug 2004
Analysis Of Mass Spectral Data In The Quiet Zones	10/999,638	24 Nov 2004

Preparation Of Biologically Derived Fluids For Biomarker Determination By Mass Spectrometry	11/051,807	04 Feb 2005
Determination of Analyte Characteristics Based Upon Affinity Binding Properties	11/069,277	01 Mar 2005
Isobaric-Coded Mass Tags for Quantitative Protein Analyses with Tandem MS	11/179,060	11 Jul 2005
Methods, Compositions and Kits Pertaining To Analyte Determination	11/319,685	28 Dec 2005
Isobaric-Coded Mass Tags for Quantitative Protein Analysis with Tandem MS	11/355,904	15 Feb 2006

V. RESPONSE TO THE OFFICE ACTION REJECTIONS

1. **Rejection for Obviousness-Type Double Patenting**

As previously discussed, since both patent applications remain pending, claims of one or both applications can be amended and/or canceled. Accordingly, this provisional rejection should be held in abeyance until such time as both patent applications contain allowable subject matter or in the alternative until this application is determined to have otherwise allowable subject matter that conflicts with pending claims of the other patent application. At such time, Applicants can reconsider the requirement for a terminal disclaimer or cancel the offending claims.

Notwithstanding the foregoing, Applicants disagree with the Examiner's statement that: "*new claim 71, which is drawn to a morpholine and not a piperazine.*" (OA at page 4) It is believed that new claim 71 is drawn to morpholine and piperazine compounds and now, as amended as discussed during the personal interview on May 25, 2006, also pertains to piperidine compounds. New claims 73-74 are added to bring clarity to this issue.

2. **New Rejections under 35 U.S.C. § 112, Second Paragraph**

a) *The Law Of 35 U.S.C. § 112, Second Paragraph*

Claims are not analyzed in a vacuum. *In re Moore*, 58 C.C.P.A. 1042, 1047, 439 F.2d 1232, 1235, 169 U.S.P.Q. 236, 238 (Cust.&Pat.App., 1971). In footnote 2, the court stated: "*It is important here to understand that under this analysis claims which on first reading -- in a vacuum, if you will-- appear indefinite may upon reading of the specification disclosure or prior art teachings become quite definite.*" *Id.*, 169 U.S.P.Q. at 240. Thus, it is well settled that a claim is sufficiently definite for purposes of the second paragraph of 35 USC § 112 if one

of ordinary skill in the art would understand what is claimed when considered in light of the specification and the prior art. *Penda Corporation v. United States*, 29 Fed.Cl. 533, 554 (1993). "A phrase is not indefinite merely because the specification does not define it" *Id.* The second paragraph of 35 USC §112 requires only reasonable precision in delineating the bounds of the claimed invention. *United States v. Teletronics, Inc.*, 857 F.2d 778, 786, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988).

b) *Discussion*

At page 5, claim 71 is rejected under 35 U.S.C. §112, second paragraph as being incomplete. At the end of the paragraph, the Examiner suggests that CJ_2 might possibly have been intended to be stated as $C(J)_2$. It is respectfully submitted that in the context of the specification, it is clear to the ordinary practitioner that the variable J attached to the "carbon of the heterocyclic ring" can properly be stated as CJ_2 just as CH_2 would be proper if J were hydrogen (and indeed this is one possibility). Regardless, Applicants agree with the Examiner's suggestion that $C(J)_2$ can be used for clarity and have amended the claim accordingly. However, it is respectfully submitted that while said amendment clarifies the claim language, it does not reduced its scope.

At page 5, claims 3 and 4 are rejected for reciting the limitation "one or more substituents". Based upon the amendment to claim 71, it is believed that the claim is sufficiently clear that the limitation "one or more substituents" refers to the whether or not each J is hydrogen or a substituent (e.g. an alkyl, an alkoxy or an aryl group – see claim 4). Moreover, the variable W, is clearly intended to be an ortho, meta or para group that is substituted for a carbon of the heterocyclic ring such that the heterocycle can be, for example, a morpholine or piperazine as repeatedly discussed in the specification and shown in various structures illustrated in the specification and figures. Regardless, claim 71 has been amended so that the group W is in the para position only as discussed during the personal interview on May 25, 2006. In brief, it is believed that claims 3 and 4 are sufficiently clear as presently claimed when viewed in light of the specification (See for example, page 28, line 14 to page 32, line 3) and the present amendment to claim 71.

At page 5, claim 10 is rejected for reciting the limitation “*wherein the compound is a salt*”. Based upon the amendment to claim 71, it is believed that this rejection is rendered moot.

At page 5, claim 8 is rejected for reciting the limitation “*wherein the six membered heterocyclic ring comprises one or more nitrogen, oxygen or sulfur atom.*” It is respectfully submitted that since W is NH, N-R¹, N-R², P-R¹, P-R², O, C or S, it is clear that the heterocyclic ring can comprise one or more nitrogen, oxygen or sulfur atoms. Contrary to statement at page 5 suggesting that claim 71 is drawn to a piperidine ring¹, it is believed that claim 71 is drawn to morpholine and piperazine compounds, and now also piperidine compounds as it has been amended.

At page 6, claim 11 is rejected for reciting the limitation: “*wherein the compound is a mono-TFA salt, a mono-HCl salt, a bis-TFA salt or a bis-HCl salt.*” Based upon the amendment to claim 71, it is believed that this rejection is rendered moot.

At page 6, claims 20, 33 and 46 are rejected for reciting the limitation: “*methoxy*”. It is believed that the amendments to claims 20, 33 and 46 render this rejection moot.

Reconsideration of all claims, as amended, and withdrawal of each rejection under 35 U.S.C. § 112, second paragraph is requested.

3. Rejections under 35 U.S.C. § 102

(a) Statement Of The Law Of 35 U.S.C. § 102(b)

It is well settled that to be anticipated, a prior art reference must teach each and every element/limitation of the claimed subject matter. M.P.E.P. § 2131. Moreover, the elements must be arranged as required by the claim. *Id.* “**The identical invention must be shown in as complete detail as is contained in the claim**” *Id.* quoting from *Richardson v. Suzuki Motor Co.*, 868 F2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

(b) *Banasiak et al. Does Not Satisfy The Test*

In the present Office Action, claims 15 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Banasiak et al. (EP 209763). Applicants traverse the rejection.

¹ The assertion on page 5 of the Office Action that claim 71 is drawn to only piperidine compounds seems to conflict with the statement on page 4 that: “*new claim 71, which is drawn to a morpholine and not a piperazine.*”

Included with this response is an English translation of EP 209730. It is respectfully submitted that Banasiak et al. does not teach all of the elements of the claimed subject matter arranged as required by the claim. In particular, it seems apparent that Banasiak et al. does not teach, at least, the element of an "*N-substituted morpholine acetic acid active ester [that] is isotopically enriched with one or more heavy atom isotopes.*" (See claim 15) Accordingly, there can be no anticipation. Reconsideration and withdrawal of the rejection of claims 15 and 20 under 35 U.S.C. § 102(b) is respectfully requested.

(c) *Sawayama et al. Does Not Satisfy The Test*

In the present Office Action, claims 41, 44 and 46 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sawayama et al. (JP 01125357). Applicants traverse the rejection.

Included with this response is an English translation of JP 01125357. It is respectfully submitted that Sawayama et al. does not teach all of the elements of the claimed subject matter arranged as required by the claim. In particular, it seems apparent that Sawayama et al. does not teach, at least, the element of an "*N-substituted piperazine acetic acid active ester [that] is isotopically enriched with one or more heavy atom isotopes.*" (See claim 41) Accordingly, there can be no anticipation. Reconsideration and withdrawal of the rejection of claims 41, 44 and 46 under 35 U.S.C. § 102(b) is respectfully requested.

4. Reconsideration of method claims under *In re Ochiai*

As stated above, it is believed that composition claims 2-5, 8-16, 18-29, 31-42, 44-53 and 71 are allowable over the art cited in the present Office Action. Since these are composition claims, reconsideration of the related, but currently withdrawn, method claim 72 is hereby requested under the reasoning of *In re Ochiai*, 71 F.3d 1565; 37 U.S.P.Q.2d 1127 (Fed Cir. 1995).

V. SUMMARY

It is believed that this response addresses all rejections set forth in the present Office Action and the application is in ready condition for allowance. In consideration of the preceding amendments and remarks, Applicants hereby respectfully request reconsideration of all pending claims, the withdrawal of all rejections set forth in the present Office Action and issue of a Notice of Allowance by The Office.

VI. INTERVIEW

If the Examiner believes a telephonic or personal interview would advance the prosecution of the subject application, the Examiner is invited to contact attorney Gildea during business hours at the telephone or facsimile numbers listed below.

VIII. FEES

A new IDS and authorization to deduct the appropriate fee from Deposit Account 01-2213 for consideration of said IDS is being submitted herewith. Because the amendment set forth herein does not increase the claim count beyond that on which the original filing fee was paid (5 independent and 70 total claims), it is believed that there is no requirement for the payment of any additional fee. Because this response is being filed within the shorted statutory period for response, again it is believed that no fee is required for consideration of this response by the Office. If however, The Office determines that any fee is properly due for its consideration of this paper, authorization is hereby granted to charge any required fee associated with the filing or proper consideration of this paper to Deposit Account 01-2213 (Invoice No. BP0207-US3).

IX. CORRESPONDENCE/CUSTOMER NUMBER

Please send all correspondence pertaining to this document to:

Brian D. Gildea, Esq.
Applied Biosystems
500 Old Connecticut Path
Framingham, MA 01701
Telephone: 508-383-7632
Fax: 508-383-7468
Email: brian.gildea@appliedbiosystems.com

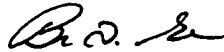
IF NOT ALREADY DONE, PLEASE ASSOCIATE THIS CASE WITH CUSTOMER
NUMBER

23544

Respectfully submitted
on behalf of Applicants,

June 8, 2006

Date



Brian D. Gildea, Esq.; Reg. No. 39,995



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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NOTICE OF ALLOWANCE AND FEE(S) DUE

23544 7590 09/20/2006

APPLIED BIOSYSTEMS
500 OLD CONNECTICUT PATH
FRAMINGHAM, MA 01701

EXAMINER

GRAZIER, NYEEMAH

ART UNIT

PAPER NUMBER

1626

DATE MAILED: 09/20/2006

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/765,267

01/27/2004

Darryl J.C. Pappin

BP0207-US 3

9577

TITLE OF INVENTION: COMPOSITIONS AND KITS PERTAINING TO ANALYTE DETERMINATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1400	\$300	\$0	\$1700	12/20/2006

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.
- B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

- A. Pay TOTAL FEE(S) DUE shown above, or
- B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
 or **Fax (571)-273-2885**

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

23544 7590 09/20/2006

APPLIED BIOSYSTEMS
500 OLD CONNECTICUT PATH
FRAMINGHAM, MA 01701

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,267	01/27/2004	Darryl J.C. Pappin	BP0207-US 3	9577

TITLE OF INVENTION: COMPOSITIONS AND KITS PERTAINING TO ANALYTE DETERMINATION

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	\$1400	\$300	\$0	\$1700	12/20/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
GRAZIER, NYEEMAH	1626	424-001810

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
 (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
 (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,267	01/27/2004	Darryl J.C. Pappin	BP0207-US 3	9577
23544	7590	09/20/2006	EXAMINER	
APPLIED BIOSYSTEMS 500 OLD CONNECTICUT PATH FRAMINGHAM, MA 01701			GRAZIER, NYEEMAH	
			ART UNIT	PAPER NUMBER
			1626	
DATE MAILED: 09/20/2006				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 43 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 43 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability

Application No.

10/765,267

Examiner

Nyeemah Grazier

Applicant(s)

PAPPIN ET AL.

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 6/8/06.
2. ☒ The allowed claim(s) is/are 2-4, 9-16, 18-29, 31-42, 44-53, 71-74 (renumbered as 1-49).
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
 - (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date 6/8/06, 7/3/06
4. ☐ Examiner's Comment Regarding Requirement for Deposit
of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413),
Paper No./Mail Date _____.
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

DETAILED ACTION
NOTICE OF ALLOWANCE

I. ACTION SUMMARY

The Amendments to the Claims and Remarks submitted to the Office on June 8, 2006 has been fully considered and will be the basis of the following Notice of Allowance.

Claims 2-4, 8-16, 18-29, 31-42, 44-53 and 71-74 are currently pending. Claims 72 was previously withdrawn and claims 73 and 74 are new claims.

II. INFORMATION DISCLOSURE STATEMENT

The supplemental information disclosure statements filed on June 8, 2006 and July 3, 2006 have been fully considered by the Examiner.

III. RESPONSE TO AMENDMENTS

A. Remarks on the Amendments to the Specification

Applicant's argument in the Remarks filed June 8, 2006 regarding the amendment to the Specification has been fully considered.

B. Remarks on the Amendments to the Claims

Applicant's arguments, see Remarks, filed June 8, 2006, with respect to the claim identifier filed in the Amendment to the Claims (Dec. 19, 2006) have been fully considered. The amendment to the claim identifier to correct the status of the claim is acknowledged.

Additionally, Applicant's arguments, with respect to the amendment of claims 20, 33 and 46 have been fully considered and are persuasive because the limitation "methoxy" has been deleted.

Next, Applicant's arguments, with respect to the amendment of claims 71 and its "salt" have been fully considered and are persuasive because claim 71 has been amended to include a salt.

Claims 3 and 4 and 8 were rejected because the claim was unclear. After consideration of the Amendments to the Claims, specifically claim 71, submitted on June 8, 2006, the rejection has been obviated.

C. Formal Matters _ Interview

Applicant states "Interview Summary prepared by Examiner Riley on May 25, 2006." Examiner believes this is in error. Please clarify.

D. Formal Matters-Status of the Claims

Applicant's arguments, see Remarks, filed June 8, 2006 with respect to claim 71 and Examiner's remarks on p. 2, paragraph I on the Action on March 20, 2006 has been considered. For clarity paragraph I states:

Additionally, Applicant request clarification as to the status of claims 28, 29, 31-32 and 34-40. As stated in the Action (March 20, 2006) and on the index of claims (PAIRS) said claims are in condition for allowance.

E. Obviousness-Type Double Patenting Rejection

Applicant's arguments, see Remarks, filed June 8, 2006, with respect to Obviousness-type Double Patenting Rejection have been fully considered. The applicant submitted a terminal disclaimer to the Office on September 11, 2006. Thus, the ODP has been obviated.

F. Claim Rejection under 35 USC 112, 2nd

Applicant's arguments, see Remarks Section 2b, pp. 20-21, filed June 8, 2006, with respect to the 112, 2nd rejection, have been fully considered and are persuasive in light of the Amendments to the claim. The rejection has been obviated.

G. Rejections under 35 USC 102

Applicant's arguments, see Remarks Section 3, pp. 21-22, filed June 8, 2006, with respect to the 102(b) rejection, have been fully considered and are persuasive. The rejection has been withdrawn because the prior art of record do not disclose isotopically enriched compounds.

H. Reconsideration of Method claims under In re Ochiai

Claims 2-4, 8-16, 18-29, 31-42, 44-53, 71, 73 and 74 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claim 72, directed to the process of making a product using the allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because claim 72, previously withdrawn from consideration under 37 CFR 1.142 in the Action filed March 20, 2006, has been rejoined. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claims including all the limitations of an allowable product claim or rejoined process claim are presented in a continuation or divisional application, such claims may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

IV. REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The instant invention is drawn to compounds pertaining to analyte determination. The instant invention appears to be free of the art of record. The closest prior art reference of record is JP 01125357 A2 (Sawayama et al.). Sawayama et al. discloses 1-[1-oxo-2-[4-(phenylmethyl)-1-piperazinyl]propoxy]-@-2,5-pyrrolidinedione. However, the disclosed compound is not isotopically enriched and is therefore not anticipated nor rendered obvious by the prior art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

V. CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nyeemah Grazier whose telephone number is (571) 272-8781. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:30 a.m. - 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, can be reached on (571) 272 - 0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Very truly yours,



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Tel. No.: (571) 272-0699

Index of Claims



Application/Control No.

10/765,267

Examiner

Nyeemah Grazier

Applicant(s)/Patent under
Reexamination

PAPPIN ET AL.

Art Unit

1626

✓	Rejected
=	Allowed

—	(Through numeral) Cancelled
+	Restricted

N	Non-Elected
I	Interference

A	Appeal
O	Objected

Claim		Date									
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